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BUREAU OF HYGIENE AND TROPICAL DISEASES

TROPICAL DISEASES BULLETIN

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THE CHEMOTHERAPY OF RICKETTSIAL INFECTIONS

By G. M. FINDLAY, C.B.E., M.D., D.Sc., F.R.C.P.

Before the War of 1939–1945 there was no known drug which had any effect on rickettsial infections. Now a number of compounds of widely different chemical constitution have been found to inhibit the growth of rickettsiae in chick embryos or to influence rickettsial disease in mice. Only *para*-aminobenzoic acid and chloromycetin are known to have an ameliorative action on rickettsial infections in man ; but acridine derivatives, streptomycin, certain sulphonamide compounds and methylene blue all have a rickettsiacidal action in animals.

Not all species of rickettsiae are equally susceptible to rickettsiacidal agents. *Rickettsia burneti*, the causal agent of Q fever, for instance, is unaffected by penicillin or sulphonamides (SPICKNALL *et al.* 1947).

There is still some doubt as to the best method of determining anti-rickettsial action. Three techniques are possible :—(1) the injection of rickettsiae and drug into developing hens' eggs ; (2) intranasal instillation of rickettsiae and intraperitoneal injection of the drug in mice : counting the lung lesions ; (3) intradermal inoculation into rabbits of a mixture of rickettsiae and drug after preliminary incubation. It is probable that, as in the case of malaria, each compound should be tested in more than one host, in this case in mice or rabbits and in the developing chick embryo.

In chemotherapeutic studies the following agents have been investigated :—

(i) *para-Aminobenzoic Acid (PABA)*

The effectiveness of *p*-aminobenzoic acid (PABA) in mice infected with murine typhus was first demonstrated by SNYDER *et al.* (1942) ; they employed it on finding that sulphonamides appear to stimulate the growth of rickettsiae, since PABA is a known sulphonamide antagonist. Evidence of the action of PABA in a considerable number of rickettsial infections was subsequently obtained in many laboratories. In the yolk sac of developing chick embryos PABA or its sodium salt inhibits the multiplication of *Rickettsia mooseri* (GREIFF *et al.* 1944, HAMILTON *et al.* 1945), *R. prowazeki* (HAMILTON *et al.* 1945, HAMILTON 1945) and *R. orientalis* (SNYDER *et al.* 1947), *R. rickettsi* (HAMILTON 1945) : the susceptibility of *R. quintana*, *R. burneti* and *R. akari* is not yet known. In experimental rickettsial infections the mortality in white mice (SNYDER *et al.* 1942), gerbilles (SNYDER and ZARAFONETIS 1945, MURRAY *et al.* 1945, ZARAFONETIS *et al.* 1946), cotton rats (SNYDER *et al.* 1947), and guinea-pigs (ANIGSTEIN and BADER 1945, 1946), is considerably reduced by PABA.

In 1944, YEOMANS *et al.* obtained a favourable therapeutic effect in patients in the first week of epidemic typhus in Egypt. The figures obtained in this study have been examined statistically by SNYDER *et al.* (1947); 20 patients were treated with PABA and 19, alternate cases with those treated, were used as controls. Treated patients had shorter fever, fewer complications and a lower mortality rate than the untreated controls: these differences were significant. In the treated group, there was a significant correlation between the final score (the number of days of fever plus the number of complications) and the duration of the illness before therapy was instituted. SNYDER *et al.* (1947) also report the results of treating 60 patients suffering from typhus in the Dachau Concentration Camp in Germany in May 1945: analysis of the results shows that there were statistically significant differences between PABA-treated and untreated patients as regards duration of fever, incidence of complications and mortality. All the evidence suggests that treatment begun early in the first week of illness is more effective than treatment begun late in the same week. In Northern Nigeria, during an epidemic of typhus, MONTGOMERY and BUDDEN (1947) treated six of the worst cases with PABA: all recovered, whereas the mortality rate in the outbreak as a whole was 25 per cent.

SMITH (1946) reported the use of PABA in 29 cases of murine typhus, LEVY and ARNOLD (1946) in 6 and DIAZ-RIVERA *et al.* (1946) in 4 cases, all with apparently good results. SMITH carefully compared his results with those in 29 controls; of the treated cases, only 7 had fever for 12 days or more, whereas in 22 of 29 controls the temperature was above normal for at least 12 days: the average duration of fever in the two groups was 10·3 and 13·2 days respectively. DIAZ-RIVERA *et al.* (1946) gave total doses of 62 to 136 gm.; a dose of 2 gm. in 25 ml. of 5 per cent. sodium bicarbonate solution was given every 2 hours; subjective improvement began in from 24 to 48 hours after the beginning of treatment.

One patient suffering from Rocky Mountain spotted fever was successfully treated with PABA by ROSE *et al.* (1945). MARONEY *et al.* (1946) similarly treated one case, FLINN *et al.* (1946) obtained good results in nine out of ten patients: blood levels of 30 to 60 mgm. per 100 ml. were necessary for success. TICHENOR *et al.* (1947) used PABA in 8 children suffering from Rocky Mountain spotted fever: all recovered, but in the previous 36 patients who had not received specific treatment only 3 had died. The most striking result was in a patient who was given the drug on the third day of illness. The daily dose was 0·73 gm. per kilo of body weight in 24 hours, divided into 3 hourly doses. RAVENEL (1947) reported five cases in children and adolescents from 3 to 17 years old. The following case is typical of those treated:—

A delirious wasted boy, 17 years old, suffered from a haemorrhagic rash together with conjunctivitis, palatal exanthem and scrotal oedema. *para*-aminobenzoic acid, 2·5 gm. in 25 ml. of a 5 per cent. solution of sodium bicarbonate, was given orally every two hours for the first two days. At the end of this time, the blood concentration of PABA was only 4 mgm. per 100 ml. The dosage was then increased to 5 gm. every two hours, in 50 ml. of solution. After 24 hours, the blood level had risen to 18 mgm. and a day later to 32 mgm. per 100 ml. The temperature dropped sharply on the fifth day and was normal on the sixth when the rash faded rapidly, the mind cleared and the boy was almost well. The other four cases improved equally rapidly.

NILES and BOURNE (1948) in treating a girl aged 4½ years with PABA gave 2 gm. in 10 ml. of 5 per cent. sodium bicarbonate solution with 60 ml. of grape juice. This dose was repeated every 2 hours for 6 days. Grape juice helped the patient to retain the drug which had previously been vomited.

Successful results in the treatment of 18 cases of scrub typhus were recorded from Burma by TIERNEY (1946).

There is now general agreement that, if success is to be obtained with PABA, certain conditions must be fulfilled. Good results from PABA therapy are to be expected in epidemic, murine and scrub typhus and the same is probably true of other forms of typhus, but only when treatment is begun during the first eight days of the disease. Thus, if there is clinical or epidemiological evidence to point to rickettsiae as the cause of a particular disease, it is as well to begin PABA treatment while waiting for the diagnosis to be established by laboratory tests, provided that certain contraindications are not present.

Precisely what is the optimum concentration of PABA in all rickettsial infections is at present unknown. Some of the PABA in the body is changed into *p*-aminohippuric acid, which is inert against *R. prowazeki*, *R. mooseri* and *R. orientalis* (SNYDER *et al.* 1947) in experimental infections and probably against other rickettsial infections as well. Analyses made with Mirick's soil bacillus (MIRICK 1943) suggest that about 80 per cent. of all diazotizable substances in the serum is free PABA when the total concentration in the serum is 15 to 20 mgm. per 100 ml. In developing hens' eggs the minimum concentration of PABA required to achieve inhibition of multiplication is approximately 5 mgm. per 100 ml. for *R. prowazeki* and *R. mooseri*, but with *R. orientalis* it is at least 35 mgm. per 100 ml. SNYDER *et al.* (1947) therefore recommend that sufficient PABA should be given to attain promptly and to maintain for the entire period of the therapy a blood concentration, as free diazotizable substance measured against a standard of PABA, of 10 to 20 mgm. per 100 ml. for patients with typhus and of 35 to 40 mgm. per 100 ml. for patients with scrub typhus or Rocky Mountain spotted fever. Since PABA is rapidly excreted in the urine, the drug must be given at frequent, regular intervals during the day and night. The initial dose is roughly 0·05 gm. per pound of body weight (0·11 gm. per kilo) or 8 gm. for a patient weighing 160 pounds (72·5 kgm.). This is followed by a dose of 1 to 3 gm. every two hours day and night throughout the course of treatment. The PABA administered should be chemically pure, odourless and almost colourless in powder form. In solution a faint brown colour is present. At least equimolar amounts of sodium bicarbonate should be given with each dose of the free acid (12·5 ml. of a 5 per cent. solution of sodium bicarbonate for each gramme of PABA). The amount of bicarbonate must be varied so as to keep the urine neutral or alkaline. For convenience, the powder (PABA) is mixed with a 5 per cent. solution of sodium bicarbonate at the bedside immediately before each dose. After taking the dose the patient should be given 100 ml. or more of water to drink.

SNYDER *et al.* (1947) used a 10 per cent. solution of the sodium salt of *p*-aminobenzoic acid, adjusted to a *p*H of 7·0, for the treatment of a patient with typhus contracted in the laboratory. A 10 per cent. solution of the salt can be made up in bulk and stored in the cold for some days. No bicarbonate solution is necessary unless the urine becomes acid.

It is imperative to estimate the blood concentration at frequent intervals, particularly in patients with azotaemia and where appreciable fluctuations in fluid intake and urinary output occur from day to day. If possible, the blood concentration should be estimated every four hours during the first 24 hours, immediately before a dose of PABA. Except when renal insufficiency is present, estimations may then be limited to once in every twenty-four hours.

Intramuscular administration (the solution being sterilized by filtration through a Seitz filter) is unsatisfactory, but intravenous drip injection may be of value in patients who are unable to swallow. The rate of flow is adjusted to permit the infusion of from 25 to 30 gm. of the drug in the course of 24 hours

It is advisable to continue treatment for at least 48 hours after the temperature has become normal, otherwise both in typhus and scrub typhus the temperature may rise and in the latter condition the adenopathy may recur (TIERNEY 1946).

If the urine is acid there may be a precipitation of crystals of PABA in the kidney tubules. The *p*H of the urine should be tested with nitrazine paper at least twice daily as long as patients have measurable concentrations of the drug in the blood. Usually it is only in cases of azotaemia that more than 13 to 20 ml. of a 5 per cent. solution of sodium bicarbonate for each gramme of PABA is necessary to bring the *p*H of the urine to 7·0 or higher. Signs of renal involvement, such as azotaemia or haematuria, are less frequent and less severe in the treated than in untreated typhus patients. The urine of some patients under treatment with PABA contains reducing substance of unknown significance.

p-aminobenzoic acid is not without toxicity. In rats a single dose of 10 gm. per kilo of body weight kills 90 per cent. of immature and 45 per cent. of adult rats. The main pathological change found by ROBIN *et al.* (1947) was hyperaemia of the distal segment of the stomach. PABA added to the diet for 2 months to the extent of 4 per cent. produced no lesions in rats.

In patients, one of the main toxic symptoms is nausea with occasional vomiting. It is, however, rarely necessary to interrupt treatment for this cause, and 250 gm. have been given without evil effects. Leucopenia may be seen in some typhus patients treated with PABA. White cell counts should therefore be performed on every patient daily from the start of therapy until three or four days after its cessation. When the total white count falls below 3,000 per cmm. or the percentage of polymorphonuclear leucocytes below 25 per cent. no further treatment should be given. In each individual case, however, it is necessary to determine whether a falling leucocyte count is more serious than the withdrawal of the inhibiting effect of PABA on the rickettsiae.

There is some evidence that PABA slightly decreases the carbon dioxide combining power of the serum : possibly also it slightly and transiently impairs liver function as shown by prothrombin and cephalin-flocculation tests.

If PABA crystals appear in the urine the administration of the drug should be stopped at once ; in patients who are too weak to swallow properly, care must be taken in giving PABA by mouth. Aspiration of PABA may be followed by severe tracheo-bronchitis. The presence of renal insufficiency before treatment, or its appearance during the course of therapy, is not a reason for withholding or discontinuing PABA, provided that the blood concentration is determined frequently, that adjustments in dosage are made accordingly, and that the urine is kept neutral or alkaline in reaction.

PABA therapy is probably not indicated for typhus patients under 40 years of age if they have been adequately vaccinated against the disease (ECKE *et al.* 1945), unless they show signs of developing a very severe infection. In cases of suspected scrub typhus, PABA should be administered irrespective of any history of previous vaccination since there is as yet no satisfactory evidence that vaccines prepared from *R. orientalis* have any beneficial effect on the course of the disease in human beings.

SNYDER *et al.* (1947) found no lesions which could be regarded as evidence of poisoning with the drug in four patients who died despite adequate doses of PABA. One fatal case showed an unexplained nephrosis. Possibly PABA might be more toxic in those with severely damaged livers.

Secondary bacterial infections are not uncommon in patients with typhus. The presence of such infections does not contraindicate PABA therapy, but sulphonamides are contraindicated since their action is inhibited by PABA. They should therefore never be given during the acute febrile phase of a

rickettsial disease under PABA treatment or while measurable amounts of PABA are still present in the blood. Penicillin is obviously the drug of choice where the secondary bacterial organisms are susceptible to it. Penicillin may be used to supplement, but not to replace, PABA.

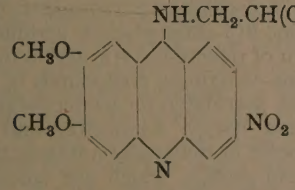
In view of its use in rickettsial infections and also because of the relationship of this compound to sulphonamide action, the pharmacology of PABA has received considerable study. Earlier investigations are reviewed by ANSBACHER (1944). According to BLOOMBERG (1946), PABA is rapidly absorbed within 8 hours from the intestine, chiefly the small intestine, but only about 50 per cent. of an oral dose is absorbed. LUSTIG *et al.* (1944), using PABA in which the nitrogen was replaced by the isotope N^{15}, found that there was no utilization or storage of the labelled nitrogen: 82 per cent. of the labelled compound was excreted 19 hours after an injection. When given by mouth, PABA appears in the urine after 8 hours: very little free PABA is present, most of it being converted to *p*-aminohippuric acid in the liver. Part of the *p*-aminohippuric acid is acetylated before excretion.

Very little is yet known of the mode of action of PABA on rickettsiae. However, at least one variety of *Neurospora* is known which requires sulphanilamide for its growth: the growth-promoting action of sulphanilamide is inhibited by PABA. LECOQ and SOLOMIDÉS (1947) have shown that PABA inhibits the growth of *Bacterium coli*. GREIFF and PINKERTON (1948) think that PABA acts by increasing the oxygen uptake of typhus-infected eggs. *Ortho-* and *meta*-aminobenzoic acid are not rickettsiastatic and do not increase oxygen uptake. BENIGNO (1947) believes that PABA depresses the body temperature so that rickettsiae cannot multiply.

Estimation of p-*aminobenzoic acid.*—Methods of estimating *p*-aminobenzoic acid in the tissues have been devized by LEWIS (1942), KIRCH and BERGEIM (1943) and PENNINGTON (1946). Microbiological assay is the simplest method, the organism used being either *Lactobacillus arabinosus* 17·5 or preferably, according to Pennington, *Leuconostoc mesenterioides*. The extent of growth after 15 hours at 37°C. is determined turbidimetrically (THOMPSON *et al.* 1943).

(ii) *Acridine Compounds*

Claims have been made that mepacrine is of value in the treatment of louse-borne typhus either when it is given alone (VAN MEERENDONK 1942a) or with calcium (VAN MEERENDONK 1942b): these results have not been generally substantiated, though in murine typhus ARBONA (1945) believed that mepacrine was beneficial. FERRO-LUZZI and FERRO-LUZZI (1947) failed to detect any good results from mepacrine intravenously in louse-borne typhus. During the war, FUSSANGER (1945) found that some acridine compounds were effective in



(I)

(II)

2,3-dimethoxy-6-nitro-9(diethyl-amino-hydroxy-propylamino)-acridine-dihydrochloride.

preventing death of mice infected with murine typhus. The most active of these compounds were 2,3-dimethoxy-6-nitro-9(diethyl-amino-hydroxy-propyl-amino)-acridine-dihydrochloride (nitroakridin 3582); and rutenol, which is an

arsenical salt of the former, 1 molecule of nitroacridine being combined with 2 molecules of *p*-glycolyl-aminophenylarsonic acid, the arsenic being attached at nitrogen atoms (I) and (II). The previous information that rutenol is composed of two parts of nitroacridine with three parts of arsenic trioxide is incorrect.

No serious toxic manifestations attributable to these drugs were noted in a number of patients who received 2·5 gm. of nitroakridin 3582 or 4·0 gm. of rutenol given in divided doses over a period of two and a half days (FUSSANGER 1945; HOLLER and ZAJITSCHEK 1944; HOLLER 1944). The reported clinical effectiveness of these drugs in the treatment of epidemic typhus and trench fever (HOLLER and ZAJITSCHEK 1944, HOLLER 1944) requires further investigation.

SMADEL *et al.* (1947a) confirmed the fact that nitroakridin 3582 and rutenol have a definite rickettsiastatic action on *Rickettsia prowazeki*, *R. mooseri*, *R. rickettsi* and *R. orientalis* in the developing chicken embryo. Acriflavine (2,8-diamino-10-methyl acridinium chloride) was active when the dose was 0·4 mgm. per egg, close to the toxic level. Mepacrine dihydrochloride in amounts up to 2·0 mgm. per egg had no effect on *R. prowazeki* or *R. rickettsi*; 4·0 mgm. doses killed all embryos.

A comparatively simple compound prepared by ALBERT *et al.* (1945), 2-nitro-5-amino-acridine, was found to be effective in doses of 0·2 mgm. per egg. This dose is as effective as 0·4 mgm. of nitroakridin 3582, but the former is more toxic as 0·4 to 0·5 mgm. doses killed one-half to two-thirds of the embryos. Proflavine, 2,8-diaminoacridine, is without chemotherapeutic effect on rickettsiae.

There is no evidence that nitroakridin 3582 and *p*-aminobenzoic acid act synergistically on rickettsiae (SMADEL *et al.* 1947b). Nitroacridine is toxic to mice in doses of 200 mgm. per kilo of body weight when given subcutaneously and in doses of 25 mgm. per kilo of body weight after intravenous injection.

The Mode of Action of Acridine Compounds.—Observations by MCILWAIN (1941 and 1942) and MARTIN and FISHER (1944) show that the bacteriostatic properties of acridines, such as acriflavine and proflavine, are inhibited by adenine-containing substances, adenine, adenylic acid, cozymase and yeast nucleic acid, as well as by certain intermediate products of the action of these substances.

FITZGERALD and LEE (1946) have shown that several of these substances counteract the inhibition of growth of bacteriophage which is displayed by acridine compounds (FITZGERALD and BABBITT 1946). SMADEL *et al.* (1947a) found that relatively large amounts of yeast nucleic acid were required to block the rickettsiastatic action of nitroakridin 3582, the ratio being 200 to 1, whereas in the case of bacteriophage the ratio, according to FITZGERALD and LEE (1946) was only 25 parts to 1 part of 2-amino-9(*p*-aminophenyl) acridinium chloride. It seems probable that the mechanism of rickettsiastatic action by nitroakridin is one of interference with the adenine-containing compounds of the organism or host cell in a manner similar to that postulated for bacteriostasis (MCILWAIN 1941 and 1942; MARTIN and FISHER 1944). ANDREWES and KING (1946) suggest that acridines inhibit the process of rickettsial multiplication by interfering with the acidic phosphoric acid groups, which are salient features of nucleic acid and certain co-enzymes. In any case, the mode of action of acridines is different from that of *p*-aminobenzoic acid. It may be noted that the minimal effective dose of nitroakridin 3582 in developing hens' eggs injected with *R. mooseri* is slightly less than that of *p*-aminobenzoic acid, though both are of the same magnitude. Thus 0·4 mgm. per egg of nitroacridine produces decided inhibition while 0·5 mgm. per egg of *p*-aminobenzoic acid is about the minimal effective dose (HAMILTON *et al.* 1945).

Nitroakridin 3582 has some action on the influenza virus and on viruses of the psittacosis-lymphogranuloma group. It is said to be active against haemolytic streptococci *in vivo* in a dilution of 1 in 250,000 and against staphylococci in 1 in 40,000.

(iii) *Antibiotics*

GREIFF and PINKERTON (1944), GREIFF *et al.* (1944) and MORAGUES *et al.* (1944) found that penicillin in large doses had some inhibitory action on the growth of the rickettsiae of murine and epidemic typhus in mice, but against Rocky Mountain spotted fever it was useless (FITZPATRICK 1945). *In vivo*, however, penicillin shows little activity, against either louse-borne typhus (YEOMANS *et al.* 1944, VAN DEN ENDE *et al.* 1946) or against scrub typhus (BLAKE *et al.* 1945). Tyrothricin had no action in mice infected with murine or epidemic typhus (VAN DEN ENDE *et al.* 1946). The effect of streptomycin on the growth of rickettsiae in eggs is more pronounced (MORGAN *et al.* 1947, SMADEL *et al.* 1947b and c). In addition to *R. prowazeki*, *R. mooseri* and *R. rickettsi*, *R. akari*, the newly recognized agent of rickettsialpox (HUEBNER *et al.* 1946), is affected by doses as small as 1 mgm. per egg. The administration of 10 mgm. per egg resulted in a distinct lengthening of life of the infected embryos. Curiously enough, *R. orientalis* is scarcely affected by streptomycin. Streptomycin has been shown to have a curative action on *R. burneti* both in the infected hen's egg and in guineapigs (HUEBNER *et al.* 1948). Dihydrostreptomycin (DONOVICK and RAKE 1947) has some general rickettsiastatic activity, but it is less than that of streptomycin. The action of streptomycin against rickettsiae is reduced by substances such as semicarbazide (RAKE and DONOVICK 1946) which also reduces the bactericidal action of antibiotics, thus suggesting that antibacterial and antirickettsial action go hand in hand.

Combined treatment of embryos infected with the four susceptible rickettsiae with 10 mgm. of streptomycin and 0·5 mgm. of *p*-aminobenzoic acid results in a more striking inhibition of growth than is obtained with similar amounts of either drug alone. In a like manner, 10 mgm. of streptomycin and 0·4 mgm. of nitroakridin display an additive effect in embryos infected with *R. mooseri* and *R. rickettsi*.

EHRLICH *et al.* (1947) showed that a *Streptomyces* obtained from the soil of a field near Caracas, Venezuela, produced an antibiotic chloromycetin which had a therapeutic effect on *R. prowazeki* in chick embryos. This was confirmed by SMADEL and JACKSON (1947) who found this antibiotic active in chick embryos against *R. prowazeki*, *R. mooseri* and *R. rickettsi* as well as in mice infected with 25 to 100 M.L.D. of *R. orientalis*. In mice 0·1 to 1·5 mgm. intraperitoneally or 1·5 to 5 mgm. orally were required to cure infection. *R. akari* was also affected in mice and in embryonated eggs. Similar results were obtained in man by PAYNE *et al.* (1948) working with epidemic typhus in Bolivia. Sixteen patients were treated either intravenously or by mouth for three days. Intravenously 10 mgm. per kgm. was given three times a day for three days while by mouth 15 mgm. per kgm. was administered without toxic effects. Three to four hours after intravenous injection there was improvement in headache, backache and vision, while after oral medication good effects were noted six to eight hours after the first dose. There were no deaths. Similar doses were given to five normal controls without any toxic effects. Recent reports suggest that chloromycetin is of value in scrub typhus in man.

(iv) *Dyestuffs*

Methylene blue was shown by OTTO and SCHÄFER (1936) to have an action on murine typhus infection in mice, a result confirmed by KIKUTH and

SCHILLING (1944) in guineapigs. PETERSON (1944) used toluidine blue with some success in murine infections in mice.

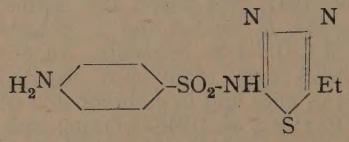
Later PETERSON and FOX (1944) and MCLIMANS and GRANT (1944, 1945 and 1947) found that both toluidine blue and methylene blue were active against *R. orientalis* in mice, while ANIGSTEIN and BADER (1945) obtained similar results in Rocky Mountain spotted fever. Both dyes are highly effective in mice in the oral maximum tolerated dose of 7·5 mgm. and in cotton rats against intraperitoneal injections of rickettsiae even when therapy is delayed until a systemic infection is well established. Methylene blue is also effective against intracerebral infections in mice, but when given subcutaneously the drug is much less active (PETERSON and FOX 1947). In mice, methylene blue appears to be more effective than *p*-aminobenzoic acid against *R. orientalis*.

ANDREWES *et al.* (1946b) tested a number of dyes against rickettsiae injected intranasally into mice and intradermally into rabbits. The results of the two tests were in close agreement. The only dyes which showed any activity were methylene blue, toluidine blue, new methylene blue and 3-diethylamino-7-di-*n*-butylaminophenaz-thionium chloride hydrochloride among thiazines and a selecazine, selenium-methylene blue. Unfortunately the good results obtained in animals have not held good in man. STEELE *et al.* (1946) found that methylene blue, largely owing to its toxicity, was without effect in scrub typhus in man. It has been found that the rickettsiacidal action of methylene blue in mice infected with *R. orientalis* is greatly enhanced if the animals are placed in an atmosphere containing 50 per cent. of oxygen (MCLIMANS and GRANT 1947). Unlike the acridines and *p*-aminobenzoic acid, toluidine blue and methylene blue are active against rickettsiae *in vitro*. Sodium nitroprusside reduces the acute toxicity of methylene blue (PFEIFFER *et al.* 1945) : unfortunately it seems to have very little action on the chronic toxic effects of the drug (PETERSON and FOX 1947).

(v) *Sulphonamide Derivatives*

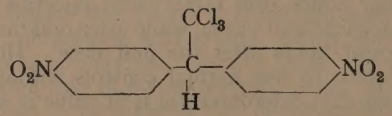
The commoner sulphonamides are without action on rickettsiae : in fact in experiments involving the adaptation of rickettsiae to mouse lung it is usual to give the mice sulphathiazole or sulphadiazine to protect them against secondary bacterial infections.

During the war, it was found that some sulphonamides were, however, active against murine typhus in mice : of these, globucid was the most effective.



Globucid

Another compound appeared to be equal to methylene blue in its action on



R. mooseri.

The most extensive series of sulphonamides, however, was that studied by ANDREWES *et al.* (1944) and VAN DEN ENDE *et al.* (1946) in mice inoculated intranasally with murine and epidemic typhus rickettsiae.

The compounds showed activity as follows :—

No.	Compound	A* mgm.	B* mgm.
V 147	*p*-Sulphonamidobenzamide hydrochloride	24	4
V 186	*p*-Sulphonamidobenzamidoxime hydrochloride	24	2
V 207	*p*-Sulphonamidobenzamidoxime (free base of V 186) ...	16	4
V 192	*p*-Sulphonmethylamidobenzamidine hydrochloride ...	16	8
V 262	*p*-Sulphonhydroxylamidobenzamidoxime base	16	4
V 279	*p*-Sulphonamido-*m*-tolamidoxime hydrochloride	16	>8
V 276	*p*-Sulphonamido-*m*-tolamidine hydrochloride	8	>4
V 231	*p*-Sulphonamidobenzamidoxime methyl ether hydrochloride	16	8
V 232	*p*-Sulphonamidobenzamidoxime ethyl ether hydrochloride	8	4
V 280	NN′-Dipropoxybenzamidine-*p*-sulphonamide	16	8
V 281	NN′-Dimethoxybenzamidine-*p*-sulphonamide	8	4
V 283	NN′-Diethoxybenzamidine-*p*-sulphonamide	8	>8
V 238	*p*-Sulphonamidobenzamidoxime ureide	8	2

A* = Max. tolerated dose for 15 gm. mouse.
B* = Minimal effective (wholly suppressive) dose given twice daily.

All the hydrochlorides in this series were readily soluble in water : the free bases were only sparingly soluble. The only compounds having a favourable ratio between toxicity and activity in mice were V 147 and V 186 : neither protected guineapigs from fever when epidemic typhus rickettsiae were injected intraperitoneally. These drugs had no *in vitro* action on rickettsiae : their activity was not abolished by *p*-aminobenzoic acid.

V 147

V 186

Two volunteers who were given 16·79 and 20·38 mgm. of V 186 in six days showed no evidence of poisoning. In animals, there was a tendency for the blood pressure to be lowered and the blood urea to be raised. When V 147 and V 186 were tested in patients with epidemic typhus in North Africa and Naples the results were disappointing. The human kidney appears to be extremely susceptible to the action of the drugs : severe degenerative changes were found in the renal tubular epithelium of fatal treated cases in Naples and a number of unexplained cases of vascular collapse made it inadvisable to increase the dose. The relation between chemotherapeutic action and chemical constitution in this group of compounds is discussed by ANDREWES *et al.* (1946a). It is possible that these amidines and amidoximes enter the cell and are built up, while nucleic acid synthesis is active, into some essential vital structure of the rickettsiae : this might possibly be through the amidine or amidoxime group, a group of which the elements occur once in every pyrimidine and twice in every purine. It is obvious that only very slight modifications of the *p*-sulphonamidobenzamidine molecule are needed to abolish rickettsiastatic action altogether. Many other sulphonamides and sulphones were devoid of action in mice inoculated intranasally. It must, however, be noted that this method of inoculation fails to demonstrate the protective action of *p*-aminobenzoic acid in mice.

(vi) *Other Rickettsiastatic Compounds*

It has been reported by DURAND and SCHNEIDER (1945) that the 4-amino-quinoline derivative sontoquine (SN 6911) is of value in cases of louse-borne typhus, but these results have not been confirmed. SMADEL *et al.* (1947b) failed to determine any demonstrable effect on the growth of rickettsiae in developing hens' eggs of several biologically active compounds, tryptophane, riboflavin, folic acid, 2-amino-4-hydroxypteridine-6-carboxylic acid and *p*-amino-benzoyl-l(+)glutamic acid. These substances did not influence the rickettsiastatic effect of *para*-aminobenzoic acid.

FERRO-LUZZI and FERRO-LUZZI (1947) found that intensive vitamin therapy shortened convalescence in typhus but the following methods of treatment were quite useless:—"Novasurol" intravenously, congo red intravenously, mercurochrome, neoarsphenamine or calcium intravenously: sulphanilamide, sulphapyridine and penicillin produced somewhat indefinite results. Sodium benzoate and sodium salicylate caused a reduction in mortality and a slight reduction in the duration of the disease, but sodium benzoate was associated with an increased liability to complications. Both drugs caused delirium, dizziness, tinnitus and signs of gastric irritation.

More definite results were obtained with aspirin. The first series consisted of 83 Eritreans and 12 Europeans: dosage was either 4 gm. (1 gm. every 6 hours) per day or 8 gm. (1 gm. every 3 hours) per day. Treatment was continued for 2 days after return of the temperature to normal. Only one death occurred among the 94 patients thus treated, whereas among the controls the death rate was 14·8 per cent.: the duration of the disease was 11·1 days in treated as against 14·8 in untreated cases, while 23·8 per cent. of the treated had complications as against 37 per cent. of the controls. In a second series treated in 1947, 74 patients were given aspirin: 112 were left as controls. The mortality among the controls was 10·7 per cent., among the treated 5·4 per cent.

Forbisen, 4,4′-*bis*-antipyrine, was shown by PETERSON (1944) to have some action on murine typhus.

VAN DEN ENDE *et al.* (1946) tested a very considerable number of alkaloids, arsenicals, aromatic amidoximes with sulphur, aromatic amidines with sulphur, aromatic guanidines, biguanidines, amidines and amidoximes with sulphone groups, pyrimidines and miscellaneous compounds, with completely negative results.

Riboflavin deficiency has been found to render the peritoneal cells of the rat susceptible to typhus and riboflavin therapy is then effective against the infection. Large amounts of riboflavin are, however, therapeutically ineffective in typhus-infected normally fed mice. In view of the importance of high vitamin therapy in typhus, it is of interest to note that in 1804 HEATH found yeast of great value in severe typhus infections. If the tissues of different species differ in their content of essential metabolites or enzymes, this may possibly explain the varying response of different species to the same chemotherapeutic agent.

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SUMMARY OF RECENT ABSTRACTS*

VI. PLAGUE

Epidemiology: Transmission

DAVIS (p. 76) describes the outbreak of plague in Ngamiland during 1944–45, which was the biggest ever recorded in South Africa. It took its origin in gerbils (*Tatera*), which are subject to epizootics of plague, and from which the

* The information from which this series of summaries has been compiled is given in the abstracts which have appeared in the *Tropical Diseases Bulletin*, 1947, v. 44. References to the abstracts are given under the names of the authors quoted and the pages on which the abstracts are printed.

infection is commonly spread to the multi-mammate mice (*Mastomys*) which make use of gerbil burrows and pick up the fleas (*Xenopsylla eridos*). These mice also approach human habitations and transfer the infection to domestic rodents, whose fleas (*X. brasiliensis*) are effective vectors to man.

Tomich (p. 996) has failed to find infection in a small number of rodents examined in the Suez Canal Zone ; there is no definite evidence that sylvatic plague exists there.

Rao (p. 816) found that field rats near a village in India where plague was endemic were very susceptible to the disease, and he therefore argues that they have not been in frequent contact with the disease, and cannot be the cause of the endemicity in that area. It therefore seems a waste to fumigate rat holes in the fields, and attention should be concentrated on the more resistant rats of the village itself.

Macchiavello (p. 519) reports a focus of sylvatic plague on the borders of Peru and Ecuador.

Miyara and his colleagues (p. 815) describe the very great epizootic of plague which exists in the wild rodents of Argentina, and several outbreaks which have occurred in man, largely as a result of handling dead rodents. Pneumonic plague has occurred, which is difficult to diagnose, and which spreads from man to man. Prevention entails education in the danger of handling wild rodents, and isolation of the patients in hospital. Sera and vaccines are not regarded as useful, and anti-rat measures, essential for towns, are not applicable to the conditions of sylvatic plague.

Humphreys and Campbell (p. 758), as a result of surveys made in Canada, point out that plague is well established in ground-squirrels in parts of Alberta and Saskatchewan. So long as it is confined to these squirrels there is not much danger to man, but if rats invade the area and become infected, the problem will be serious. Rats are well established in the towns.

Wayson (p. 899) discusses the results achieved in field surveys in the United States during 10 years, when enormous numbers of rodents and fleas were examined. One infective flea can infect a series of animals. There is no evidence that rodent carriers of subacute or chronic plague are a factor in perpetuating the disease from one season to another, but it seems likely that some form of recrudescence in the carrier of quiescent disease is necessary for carry-over by infection of fleas. Prince and Wayson (p. 816) have shown that a flea can remain alive and infected with plague in a virulent form for a period of 4 months in the nest of a hibernating squirrel ; but most of the fleas which were infected and remained alive did not retain the infection for the entire 4 months. The same authors (p. 1064) show that a squirrel in whose skin plague is introduced while the animal is in hibernation in October may awaken 4 months later and subsequently develop acute manifestations of the local lesion, and lethal bacteraemia. A flea infected in October, and placed on a healthy hibernating squirrel, can retain the infection and transmit it during the following March.

Although at one time it was assumed that fasting fleas could not live longer than one month, and therefore that a voyage lasting 80 days ruled out the possibility of introduction of plague by fleas alone, Macchiavello (p. 997) has shown that fleas taken alive in jute bags imported into Peru from India were capable of inducing plague by bite, although there was no possibility that the fleas could have received their infection during the voyage.

Perry (p. 76) and Laurie (p. 76) have written on the reproduction of the brown rat and the house mouse respectively. The papers are technical and detailed, but have a bearing on studies of the rodent hosts of plague, and indicate some of the mistakes that can be made if the subject is not studied with some care.

Aetiology

GIRARD (p. 520) indicates the importance of distinguishing between *P. pestis* and the pneumococcus in the diagnosis of plague pneumonia. Cultures should therefore be incubated at 20°–26°C., not at 26°–34°C., and for inoculation or scarification tests, guineapigs rather than mice should be used since the latter are very susceptible to the pneumococcus. This organism may exert an antibiotic action on *P. pestis*, and may prolong the incubation period to 10 days in primary plague pneumonia. In Madagascar the authorities have fixed a limit of 10 days for quarantine of contacts.

LAZARUS and GUNNISON (p. 1064) show that differentiation between *P. pestis* and *P. pseudotuberculosis* by phage action is not reliable. They also found that *P. pestis* phage acted on some strains of *Salmonella* and *Shigella*.

GIRARD and SANDOR (p. 900) have studied the toxin of *P. pestis*, a protein which may be injected as whole bacilli, or as a solution since it diffuses into liquid culture media. It is not an exotoxin. RAMON *et al.* (p. 900) show that plague toxin differs from true exotoxins in that certain antibiotic substances do not act on it.

Clinical Findings : Treatment

Although meningitis is not regarded as one of the common lesions in plague, LANDSBOROUGH and TUNNELL (p. 418) report 8 cases, all fatal, in a total of 203 cases. *P. pestis* was found in the spinal fluid in 5. In one the meningitis appeared to be primary, but in the remainder it was a sequel of bubonic disease.

SOKHEY and WAGLE (p. 418) discuss the treatment of septicaemic plague, noting that septicaemia is the most important single factor determining death or recovery. They found that sulphadiazine (4 gm. followed by 2 gm. every 4 hours for not more than 10 days) gave the best results, reducing case mortality from 91 per cent. in controls treated with intravenous iodine, to 20·9 per cent. Sulphathiazole was not so useful. The authors treated 1,604 patients in all.

SIMEONS and CHHATRE (p. 77) found sulphadiazine more effective than sulphathiazole in the treatment of bubonic plague in India.

HUANG and CHU (p. 419) note that plague bacteraemia is readily controlled by sulphonamides, especially sulphadiazine, but that viable bacteria remain unaffected within buboes, and may cause relapse.

MAGROU (p. 417) reports an outbreak of plague at Ferryville, Tunisia, in which there were 37 cases and 10 deaths. Only 2 deaths occurred in the 28 who were treated with sulphadiazine. The Girard live vaccine was given to 60,000 people.

ROUX and MERCIER (p. 207) report that three of five patients with pneumonic plague were cured by administration of 65–73 gm. sulphathiazole. This is a striking result.

ALBERTO VIDELA (p. 659) has treated several cases of plague with sulphonamides and streptomycin ; in one with signs of meningitis, intrathecal administration of streptomycin was followed by striking improvement. HERBERT (p. 713) shows that streptomycin kills *P. pestis* in culture and is an effective treatment (more so than sulphathiazole) in mice and guineapigs infected with plague.

Vaccination : Control

BAKER *et al.* (p. 712) have investigated the antigenic structure of *P. pestis*. Various fractions were isolated, one of which, a carbohydrate protein fraction, is probably the normal antigen of the intact cell, and is an " envelope " antigen. For vaccines, all the antigens should be included.

MEYER (p. 816) sums up the measures taken to control plague. Recent work indicates that success in vaccination depends rather upon the actual mass of

bacterial protein injected than on the method of preparing the dead antigens, and that organisms grown on agar and killed by formalin are effective if enough are injected and if frequent " booster " doses are given. Urban plague, except in a few areas, is no longer a major problem, but sylvatic plague may be so. It is not known why human cases are so rare, although rodent plague is so very common, in the 14 States of the U.S.A. which are affected.

Wayson *et al.* (p. 419) give the results of experiments with guineapigs which indicate that plague vaccines prepared from organisms grown at 39°C., and killed by phenol or formalin, are effective in preventing death of the animals.

In a city of 110,000 inhabitants, in India, Simeons and Chhatre (p. 77), inoculated 90,000 with a single dose of killed plague vaccine (Haffkine), in the face of an epidemic. The results were disappointing, and the authors conclude that it would be dangerous to rely on vaccination of this type, given as a single dose, and that the use of cyanogas, rat-bait and anti-flea measures is much more valuable.

The Indian Research Fund Association report on plague (p. 997) shows that plague vaccine (either casein hydrolysate or agar vaccine) deteriorates if kept at 37°C., but not nearly so much at 0°C.

Grasset (p. 419) shows that a live avirulent plague vaccine has been largely used in South Africa, and that in 24,000 persons inoculated with it, there occurred only 15 cases of plague. The vaccine can be dried at low temperatures and kept for 2 years with little loss of antigenic power. Sylvatic plague is a very great problem in South Africa.

Macchiavello (p. 78) and his colleagues (p. 713) describe the use of DDT and of the rat poison sodium fluoracetate (" 1080 ") in stopping an epidemic of plague in a city in Peru where most of the rats were *R. rattus alexandrinus* and most of the fleas were *X. cheopis*. DDT as a 10 per cent. powder was applied to the floors of all houses and left unswept for a week, and elsewhere in likely rat harbourages. Sodium fluoracetate was incorporated in bait and placed with care out of reach of children. These measures were most successful. The author notes that 10 per cent. DDT is toxic for rats (which lick their fur), and that sodium fluoracetate is toxic for fleas which suck the blood of poisoned rats. For the control of plague, Elishewitz (p. 1064) advises that places frequented by rats should be dusted with DDT, to kill fleas and their larvae, and that alpha-naphthyl thiourea (ANTU) or sodium fluoracetate should be used for the rats, but with care and by skilled operators only. DDT and the modern repellents can be used in clothing, for the protection of field workers. Gouck (p. 78) has found 10 per cent. DDT in pyrophyllite successful against fleas on rats, when it is dusted in their holes and burrows.

Reporting an outbreak of plague in Algeria, which was not pneumonic and in which no rats could be found, either alive or dead, Grenoilleau (p. 658) suggests that the disease was probably transmitted from man to man by *Pulex irritans*. Control action in such an outbreak comprises prompt detection and isolation of cases, disinsectization of patients and contacts, and daily medical supervision of contacts, as well as the other, usual, methods.

The flea *Synosternus pallidus* may be a vector of plague in Dakar, and Kartman (p. 420) has shown that DDT, either as a solution or as a dusting powder, is effective against this flea, when applied in huts.

Charles Wilcocks

RABIES

OTTEN, L. **Investigations into Rabies. II.** *Antonie van Leeuwenhoek J. Microbiol. & Serol.* 1947, v. 13, Nos. 2/4, 101–27, 1 fig. [21 refs.]

In this posthumous contribution of the late Prof. OTTEN detailed reference is made to the statistical and experimental work on rabies carried out by his deceased wife Maria J. OTTEN-VAN STOCKUM at the Pasteur Institute, Bandoeng, Netherlands East Indies.

The following paragraphs summarize the more important conclusions reached during a prolonged period of research :—

The rate of mortality from rabies during or after treatment provides no reliable index of any particular treatment's efficacy, the sole criterion in this respect being a reduction in the occurrence of " failures ", defined as cases in which symptoms appear more than 30 days after treatment has begun.

Monkey brain furnishes a more active antigen than rabbit or sheep brain ; and in anti-rabies immunization the superiority of monkey brain fixed virus (both living and formolized) over other vaccines is evidenced by the subjoined comparative results :—

Method of treatment and when practised	No. of persons treated	No. of deaths	Percent. mortality	No. of failures	Percent. failures
Pasteur's method (1895–1905)	1421	9	0·56	7	77·7
Högyes' method (1906–1916)	1610	4	0·25	1	25·0
Monkey brain F.V. (living and dead) (1916–1940)	2919	2	0·07	0	0·0

At Bandoeng during a 25 years' period there was no " failure " among persons treated in the first week after the bite, whether with living (1916–32) or with killed, formolized (1933–40) monkey brain F.V. The vaccine most recently employed derives from a 10 per cent. suspension of monkey brain, in a 1·5 per 1,000 concentration of formalin, heated for 5 days at 37°C. Prior to its administration it is diluted to 2 per cent. and the total quantity injected, over a 14 or 21-day period, is 1,120–1,520 mgm., as against 470 mgm. of the living virus vaccine previously in use.

Two weeks' treatment was found to be as effective as a 3 weeks' course, when judged by the " failure " rate and the rabicidal antibody content of vaccinated persons' sera.

The fact that the average period of incubation in cases of rabies treated with formolized vaccine shows a definite shortening, when compared with those treated with live vaccine, not only disproves the statements of NITSCH (*Cent. f. Bakt.* I. Abt. Orig., 1906, v. 42, 647, 775) and of PROCA and BOBES [this *Bulletin*, 1940, v. 37, 618] that the shortening is to be ascribed to the action of living F.V., but also encourages the hope that by the use of formolized vaccine the immunization process will attain its maximum more rapidly—within the first 30 days following the commencement of treatment, *i.e.* within the defined " failure " limit—and effect a greater reduction in mortality.

Formolized vaccine, when prepared as a 2 per cent. suspension and sorted at room temperature, rapidly lost potency ; stored as a 10 per cent. suspension at 5°C., however, it showed no appreciable decrease in activity. Decentralization

of treatment is thus possible if the original 10 per cent. suspension, preserved regionally under adequate storage conditions, is diluted to 2 per cent. immediately before its administration.

The testing of a 10 per cent. suspension before and after centrifuging showed that both in virulence and antigenic activity the supernatant fluid was much inferior to the ordinary suspension and to the deposit.

An experiment devised to ascertain whether, over a 14-day period, the immunization of the rabbit and the guineapig (in a total dosage of 20 mgm. and 10 mgm. respectively) could better be effected by consecutive daily injections of slowly increasing strength or by three adequately interspaced injections of increasing strength failed to show any difference in favour of the daily injection.

G. Stuart

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Irr, G. La prophylaxie de la rage. Police sanitaire et vaccination préventive. [**Prophylaxis against Rabies. Sanitary Control and Preventive Inoculation.**] *Cahiers Méd. Union Française.* Algiers. 1947, Oct., v. 2, No. 13, 615–31. [12 refs.]

The author deplores the comparative failure in France and in French North Africa of the sanitary regulations prescribed for the prevention and control of rabies. He attributes this failure, not to the inadequacy of the regulations themselves, but to the fact that the requisite powers of enforcement are vested in local rather than in central authority. He compares the state of affairs in France unfavourably with that in Great Britain, where similar legislative measures have been enforced by central authority (the Ministry of Agriculture) since 1899.

In discussing the actual measures to be adopted the author urges large-scale vaccination of dogs—free of charge to the owners—and goes so far as to state that vaccinated dogs are no longer susceptible to rabies.

He proposes the adoption of a specific programme for Algeria and includes therein a suggestion whereby the practice of canine prophylaxis may be stimulated, *viz.*, a relaxation in the case of vaccinated dogs of sanctions otherwise immediately imposed by the law. Thus a vaccinated dog having been in contact with an animal suspected of rabies would be subject to surveillance at home instead of to summary destruction. (Such leniency contrasts sharply with the measure in force which prohibits dogs from appearing on public thoroughfares unless muzzled and on the leash.) He further recommends that dog shows should be open only to those animals vaccinated against rabies.

Other measures in common practice elsewhere are also dealt with in the paper : the impounding and destruction of all stray dogs, the compulsory wearing of collars with ownership clearly indicated.

The author feels confident that the adoption of such a programme, coupled with the transfer of overall powers of enforcement from the communes to the prefectures would materially improve the far from satisfactory rabies situation existing in Algeria today.

G. Stuart

Remlinger, P. & Bailly, J. La rabia del lobo. Criterio de la vacunación pasteuriana. [**Wolf Rabies and the Assessment of Pasteurian Vaccination.**] *Med. Colonial.* Madrid. 1948, Mar. 1, v. 11, No. 3, 115–18.

MALARIA

PELLICCIOTTA, R. Note sulla morbilità malarica nella zona Dire-Daua-Errer dell'Etiopia. [**A Note on Malaria Morbidity in the Dire-Daua-Errer Area of Ethiopia.**] *Acta Med. Italica.* 1948, Jan., v. 3, Supp. No. 1, 25–6.

The English summary appended to the paper is as follows :—

"The author has studied the malaria morbidity in the region of Dire-Daua-Errer in Ethiopia, observing, in many subjects, many of them without temperature, presence of many malaria parasites in the blood.

"He calls attention to the high endemicity of the malarial infection in that region."

DALAL, P. A. **Bombay and its Malaria.** *Indian J. Med. Sci.* 1947, Dec., v. 1, No. 6, 275–91. [11 refs.]

In this lecture the author refers to the outstanding epidemics of malaria that have afflicted Bombay City in the past ; to the numerous surveys and special investigations that have shown how the disease might be controlled, or even eradicated, at no prohibitive cost ; and the failure of the authorities to take effective steps to that end. No new facts are adduced but information regarding the local habits of the only vector, *A. stephensi*, is well summarized.

Norman White

ESTELA GASTELO, Manuel A. Encuesta malárica de reconocimiento del Valle de Cañete. [**Malaria Survey of the Cañete Valley.**] Publicaciones de la Dirección General de Salud Publica, Departamento de Malaria. 86 pp., 2 maps, 4 charts & 8 plans. [14 refs.] 1947, Feb. Lima, Peru.

The Cañete Valley is the southern part of the Province of the same name which forms the south-eastern part of the Department of Lima. The Valley covers an area of 21,800 hectares ; its mean altitude is 96 metres above sea-level. Its estimated population is 31,710. The Valley, watered by the River Cañete, has a maximum width of 20 km. ; elsewhere its width varies from 13 to 17 km. It is very fertile. The geography, hydrography, geology and agriculture of the Valley are outlined and information is given about the social and economic conditions of the population. Pneumonias, pulmonary tuberculosis and enteritis are responsible for most deaths. Deaths attributed to malaria have declined markedly during the last decade. The malaria death rate in 1944 was 1·49 per thousand (49·32 per thousand all causes) : 3,816 cases of malaria were reported with 18 deaths. Malaria is most prevalent during the first seven months of the year.

In November and December 1945, 2,210 children below the age of 12 were examined ; 295 (13·3 per cent.) had enlargement of the spleen. In 101 of these the spleen was palpable only on deep inspiration ; in 117 others it did not extend beyond the costal margin ; in 20 the spleen reached the umbilicus.

The blood of 2,167 of these children was examined ; parasites were found in 107 (4·9 per cent.). The percentage incidence of parasite species was *P. vivax* 54·2, *P. falciparum* 34·4 and *P. malariae* 11·4.

Only two species of *Anopheles* were found, *A. pseudopunctipennis* and *A. punctimacula*. The former is the chief vector of malaria ; it is widespread, markedly anthropophilic and frequents human habitations. *A. punctimacula* was only rarely found breeding and only occasionally captured in dwelling houses ; it too shows a predilection for human blood but its rôle as a malaria vector has yet to be defined.

Norman White

KETTLE, D. S. & SELLICK, G. **The Duration of the Egg Stage in the Races of *Anopheles maculipennis* Meigen (Diptera, Culicidae).** *J. Animal Ecology.* 1947, May, v. 16, No. 1, 38–43, 2 figs. [12 refs.]

Wild-caught females of various races of *Anopheles maculipennis* were allowed to oviposit in small cages and the times of hatching of the eggs were observed. The data presented in this paper were collected in Italy in the spring of 1945 and analysis shows that at 10°C. eggs of *A. m. maculipennis* develop more rapidly than do the eggs of either *A. m. labranchiae* or *A. m. melanoon*, but the difference becomes less at higher temperatures until at about 20°C. it is negligible. The following examples are extracted from a table of mean incubation periods: eggs of *A. m. maculipennis*, 10 days at 10·6°C., and 4 days at 16·5°C.; eggs of *A. m. labranchiae*, 12·6 days at 10·6°C., and 4·2 days at 17·3°C.; eggs of *A. m. melanoon*, 12 days at 10·8°C. and 4·5 days at 17·0°C.

The authors suggest that the quicker development of the eggs of *A. m. maculipennis* at the lower temperatures is possibly an adaptation to the more rigorous climate to which this race is exposed in its natural habitat, as compared with that of the other races. *H. S. Leeson*

KARTMAN, L., NEWCOMB, E. H., CAMPAU, E. J. & MORRISON, F. D. **Mosquitoes collected in Dakar, French West Africa, incidental to Army Malaria Surveys.** *Mosquito News.* 1947, Sept., v. 7, No. 3, 110–15.

WHITE, R. Senior. **An Analysis of a Series of Night Catches of Anopheles.** *J. Malaria Inst. of India.* 1946, Dec., v. 6, No. 4, 417–23.

These catches of anophelines were made in 5 localities outside the control area of the Korea Coalfield in the Hazaribagh Ranges in Central India. The catches were made for the first twenty minutes of each hour from 11.0 p.m. till daylight, six times a month for 21 months.

Eleven species were obtained, but only three were collected in sufficient numbers to merit tabulation, *A. culicifacies*, *A. fluviatilis* and *A. subpictus*.

A. culicifacies shows maxima in May, August and October. Hourly incidence decreased steadily from 23.00 to 5.00 hours and was followed by the usual increased entrance before dawn.

Captures of *A. fluviatilis* were almost confined to October and November, when they represented 92 per cent. of the year's total. Prevalence of this species was highest before midnight and decreased till the pre-dawn entrance.

Dissections have hitherto incriminated only *A. fluviatilis* as a vector of malaria in this part of India. Malaria transmission, however, is active between July and September when this species is all but absent. *A. culicifacies* is probably responsible for this, in spite of the failure of dissections to confirm it. *Norman White*

REID, J. A. **Type Specimens of Culicidae described by Laveran (Diptera: Culicidae).** *Proc. Roy. Entom. Soc. of London.* Ser. B. Taxonomy. 1947, Aug. 15, v. 16, Pts. 7/8, 86–91. [12 refs.]

The author has been able to examine the original type specimens of six species of mosquitoes (two from Oceania and four from Indo-China) described by Laveran in 1901–1902. Perhaps the most interesting discovery relates to the identity of *Anopheles farauti*, a member of the *punctulatus* group, occurring in the New Hebrides. Examination of Laveran's original material shows that *A. farauti* as defined by Knight and other recent American authors is identical with Laveran's original material. For this information all students of this difficult group will be grateful. *P. A. Buxton*

MACKERRAS, M. J. & ROBERTS, F. H. S. **Experimental Malarial Infections in Australasian Anophelines.** *Ann. Trop. Med. & Parasit.* 1947, Dec., v. 41, Nos. 3/4, 329–56, 9 graphs. [24 refs.]

This investigation was undertaken in 1943 at Cairns, North Queensland, for the purely practical purpose of discovering the most useful mosquito to employ in the laboratory study of malaria transmission. The breeding and infecting of anophelines was done on a very large scale; 233,000 engorged mosquitoes were used, 38,000 dissections were performed and 20,000 infected bites were inflicted. Seven species were from Queensland, *Anopheles punctulatus farauti*, *A. annulipes*, *A. amictus amictus*, *A. amictus hilli*, *A. meraukensis*, *A. bancrofti bancrofti* and *A. stigmaticus*; two were from New Guinea, *A. punctulatus punctulatus* and *A. longirostris*. A colony of *A. p. punctulatus* was eventually established, as supplies of the other species became insufficient; this colony flourished successfully until the work ceased in 1946.

The techniques of collecting, rearing, feeding and infecting the mosquitoes are described. The characteristics which influence an anopheline mosquito in malaria transmission were studied. One of these, abundance, was satisfied in the laboratory by *A. p. punctulatus* as it colonized so readily that adequate numbers were always available. All species would feed on man, but *A. p. punctulatus* was more avid for human blood than the others; *A. stigmaticus* and *A. longirostris* would feed only with reluctance. The authors regard longevity as a most important factor in laboratory work, perhaps even more so than willingness to feed. *A. p. punctulatus* was the longest-lived species; it needed a humid atmosphere and a temperature about 70° to 75°F. (21° to 24°C.), and not less than 6 cubic inches of space per mosquito. It needed also freedom from disturbance for it was found that overcrowding and frequent handling of the cages shortened life by keeping the insects in a state of abnormal activity. The two rare species *A. longirostris* and *A. stigmaticus* showed evidence of relative insusceptibility to infection. All the common species were highly susceptible though there were, of course, individual variations in all species.

Finally, a most careful study of *A. p. punctulatus* showed that this species was the most useful in transmission experiments, in all respects. There was, however, no marked difference between *A. p. farauti* and *A. annulipes* in the laboratory studies, though the former is an important natural vector while the latter is not. *H. S. Leeson*

STAGE, H. H. & GILLETTE, H. P. S. **Observations on Mosquitoes and Malaria Control in the Caribbean Area. Part III—Trinidad.** *Mosquito News.* 1947, Dec., v. 7, No. 4, 157–9, 2 figs.

Fifteen species of *Anopheles* are known to occur in Trinidad and Tobago, of which the following five species are common: *A. aquasalis*, the most important malaria vector, *A. bellator*, an important vector in the heavy rainfall zones, *A. neomaculipalpus* and *A. albitarsis*, both suspected as minor carriers and *A. oswaldoi* a zoophilic species.

Catches in Shannon dawn traps have proved that *A. aquasalis* has migrated inland over rough country as far as five miles from its salt marsh breeding places.

In the cacao estates, tall shade trees called immortelles (*Erythrina* spp.) are interplanted. These immortelles support a considerable flora of sun epiphytes, of which the bromeliads are most numerous. The common bromeliad (*Gravisia aquilega*) breeds enormous numbers of *A. bellator*.

The difference between the leaves of bromeliads, cacao and immortelles has made it possible to use several chemical sprays as bromelicides. Best results

have been obtained with 0·5 per cent. copper sulphate and plans have been made to replace the immortelles with other trees as wind breaks, so that with the eradication of the breeding places of *A. bellator* endemic bromeliad malaria should disappear from Trinidad. *H. S. Leeson*

GABALDON, A. & COVA-GARCIA, P. Zoogeografia de los anofelinos en Venezuela. I. Los dos vectores principales. [**Principal Anopheline Vectors in Venezuela.**] *Tijeretazos sobre Malaria.* Venezuela. 1946, Mar., v. 10, No. 1, 19–32, 4 figs. [25 refs.]

Geographical distribution of *A. albimanus* and *A. darlingi* in Venezuela.

KIVITS, M. Infection malarienne à *Pl. vivax*. [**Relapsing *P. vivax* Malaria.**] *Ann. Soc. Belge de Méd. Trop.* 1947, Sept. 30, v. 27, No. 3, 333–5.

The author returned on leave from the Belgian Congo in September 1946, after 8 years' continuous residence : during that time he took daily prophylactic quinine regularly (0·3 to 0·4 gm.). He had occasional light attacks of malaria.

On his arrival on leave, on September 15, he had completed a suppressive course of quinine (1 gm. daily for 15 days). At the end of September he had a typical tertian ague, which was treated with quinine (0·25 gm. three times the first day, then 1·5 gm. daily for 5 days and 1 gm. for 8 days.)

Towards the end of October, he had another attack, again treated with quinine (1·5 gm. daily for 4 days), followed by mepacrine (0·1 gm. three times daily for 5 days). A third attack occurred in December (similarly treated), and a fourth in January : the latter was mild and responded well to quinine. The author had a mild febrile attack in February, and in March yet another appeared. He then procured some Paludrine and took the recommended dosage of 3 tablets of 0·1 gm. daily for 10 days. He took 15 days' holiday in the country and felt better than he had during the first six months of his leave.

In the middle of May, 6 weeks after the course of Paludrine, he developed another attack : having no Paludrine at hand, he used quinine again. On this occasion blood films showed many amoeboid forms of *P. vivax*, showing the " tenacity of the infection and the failure of the ' suppressive course ' of Paludrine ".

After this attack was treated with quinine [dosage not stated] together with Stovarsol, the author took Paludrine again in a dose of 1 tablet twice weekly for 6 months. He notes that his wife had attacks comparable to his own, with relapses throughout their leave. She, however, took the first " suppressive course " of Paludrine in the form of 30 tablets in 15 days instead of in 10 ; her relapse occurred five days after that of her husband.

The author points to the importance of recognizing relapsing *P. vivax* infection in persons returned from the Tropics and of the need for a prolonged course of Paludrine. *H. J. O'D. Burke-Gaffney*

KONINKLIJKE VEREENIGING INDISCH INSTITUUT (voorheen Koloniaal Institut) Amsterdam. Mededeeling No. 70. Afdeeling Instituut voor Tropische Hygiëne No. 17. De behandeling van malaria met kinine met de techniek van het bloedonderzoek door Dr. C. W. F. WINCKEL. [**Treatment of Malaria with Quinine. Blood Examination.**] 46 pp., 6 figs. & 6 coloured pls. [Refs. in footnotes.] 1947, Amsterdam : Indisch Instituut.

Doctors have to be on the alert to recognize and to treat malaria because so many persons returning from Netherlands India and from confinement during Japanese occupation are arriving in Holland. This brochure is simply and clearly set out for the use of those who are not familiar with the subject in the

home country. Quinine treatment is stressed particularly, for quinine is regarded as an essentially national medicine. The short cure is advocated and, as example, this may be given for benign tertian malaria :—A dose of quinine hydrochloride or quinine sulphate of one gramme daily is administered until the temperature is normal and then one gramme daily is given in continuation for 5 days. This usually means a total treatment of 6 to 8 days. If a relapse occurs, precisely the same treatment is carried out and so with each relapse. No advantage is claimed for quinine hydrochloride or bisulphate, which are more soluble, over the less soluble quinine sulphate. Diagrams are given to explain the method of intramuscular administration and a series of six coloured plates at the end show for *P. vivax, malariae, falciparum* and *ovale* the stages from young rings, through amoeboid forms with Schüffner stippling, schizont and morula, to male and female gametocytes. Three of the plates are those of thick drop appearances and a final table sets out differentially the appearance of each species of malaria parasite in stained films.

W. F. Harvey

STRAHAN, J. H. **Quinine by Continuous Intravenous Drip in the Treatment of Acute Falciparum Malaria.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 669–76. [20 refs.]

During the Japanese occupation of Malaya, the author was able to observe the records of nearly 2,000 cases of acute *Plasmodium falciparum* malaria in malnourished British, Australian and Dutch prisoners near Singapore. Treatment was based on quinine followed, so long as stocks lasted, by mepacrine and plasmoquine ; severe infections were treated with quinine by intramuscular or intravenous injection—the latter almost entirely by standard methods. This paper records clinical and parasitological details of 15 patients treated by a continuous intravenous drip technique.

Approximately 1,000 cases were seen between February 1942 and September 1944 ; the majority were in 1942, one of the worst periods of malnutrition. No record of the number of intravenous injections is available, but it is small. Solution for injection contained 1 grain of the bihydrochloride in 2 cc. of saline, the rate of injection being 2 cc. a minute, and the usual single dose 0·5 to 0·66 gramme. Four fatalities which were apparently due to this method, are recorded, namely :—

1. Heavy infection with *P. falciparum* : intravenous injection, 0·5 gm. ; immediate epileptiform convulsions and death.

2. Very heavy infection with *P. falciparum* : intramuscular quinine, 0·66 gm., followed in 1 hour by 0·2 gm. intravenously 20 minutes later, collapse and death.

3. Moderate *P. falciparum* infection : died during an intravenous injection (dose not given).

4. Heavy *P. falciparum* infection : 1·0 gm. quinine intravenously in 5 cc. water. Immediate epileptiform convulsions and death [a large and concentrated dose].

In addition, there was a case of *P. vivax* malaria in which during mepacrine treatment a convulsion occurred and death followed immediately after 0·25 gm. quinine intravenously.

Approximately 1,000 other cases were admitted between October 1944 and September 1945. Usually all these with over 100 parasites per thick field (Field's method) were given a preliminary intramuscular injection of 0·5 gm. quinine. When the thick film showed considerably more than this number, a parasite count was made. Where this was over 300,000 parasites per cmm. (estimated by total red cell counts and the number of trophozoites per 100 red

cells) intravenous drip quinine was given regardless of the clinical condition, and also where cerebral or other pernicious signs were present.

A Soluvac or Vacolite gravity flask, with drip regulator and tied-in cannula was used. The vehicle was sterile normal saline, sometimes with an intravenous preparation of thiamin added. In each case, 2 gm. of quinine bihydrochloride were given in 24 hours, 0·5 to 0·66 gm. per litre. The rate of flow was 30 to 40 drops per minute. The long saphenous vein at the ankle was chosen for injection, to allow use of the arms. The leg was placed on a back splint with a footpiece. The drip was continued for 12 to 96 hours, according to the severity of the case: 15 cases so treated are described in detail. The advantages of this method were: (*a*) ease of combination with other treatment; thus 2 patients received 600 cc. of blood for gross anaemia; (*b*) certainty of complete absorption; (*c*) certainty of a constant safe concentration of quinine without degeneration products producing inefficiency; (*d*) absence of unpleasant after-effects.

The disadvantage was some mild phlebitis of the vein when the cannula was *in situ* for 2 or 3 days, with risk of severe septic phlebitis.

Of the 15 patients so treated two died, one on the 3rd day from tonic spasm, 3 hours after starting the drip, the second from pyaemia due to sepsis at the site of the drip on the 28th day. This patient on admission had 1,240,000 parasites per cmm. of blood, while four had over 500,000, and all were in very poor condition.

Field and Niven [this *Bulletin*, 1937, v. 34, 615] in an analysis of 750 cases of *P. falciparum* malaria on the 1st day of treatment concluded that 750,000 parasites per cmm. in the peripheral blood was about the extreme limit of tolerance in Asian adults for the Malayan strain, and Field in a series of 2,000 cases records no recoveries where the count exceeded this figure (unpublished). A combination of starvation with a heavy malarial infection is very dangerous; Fernando and Sandarasagara in Colombo [*ibid.*, 1936, v. 33, 687] found that intravenous quinine was contraindicated when the systolic blood pressure was below 90.

The author considers that the drip method of using intravenous quinine in a dilute form sufficient to secure administration of 2 gm. in 24 hours is a safe and efficient one. Recovery is recorded of 3 cases with a peripheral intensity of infection higher than has been hitherto recorded in Malaya (871,000, 925,000, and 662,000 parasites per cmm. respectively). *C. F. Shelton*

Jailer, J. W., Rosenfeld, M. & Shannon, J. A. **The Influence of Orally Administered Alkali and Acid on the Renal Excretion of Quinacrine, Chloroquine and Santoquine.** *J. Clin. Investigation.* 1947, Nov., v. 26, No. 6, 1168–72. [11 refs.]

Haag *et al.* (*J. Pharm. & Exper. Therap.*, 1943, v. 79, 136) found that the urinary excretion of quinine given orally in a single dose was related to the *p*H of the urine, the output being increased if it were made acid. Other authors [this *Bulletin*, 1945, v. 42, 780] have drawn attention to the correlation between urinary output of quinacrine (atebrin, mepacrine) and ammonia. The effect of alkali and acid given by mouth on the urinary excretion of quinacrine, chloroquine and santoquine (the two latter being antimalarials of the 4-amino quinoline series) has now been investigated. The patients were in the older age groups and the drugs were given orally in high initial dose on the first day, followed by a smaller maintenance dose on several succeeding days till the plasma levels were fairly constant. Sodium bicarbonate was given during the day in seven doses of 2·5 gm. and a similar dose during the night (total 20 gm.), which raised the *p*H of urine to 7·5 or 8. Ammonium chloride, as the acid, was given at

similar intervals in 1·0 gm. doses (total 8 gm. daily), which made the urinary *p*H 4 or 5.

The methods of BRODIE and collaborators [this *Bulletin*, 1944, v. 41, 453 ; 1947, v. 44, 793] were used to estimate the drug concentrations in plasma and urine, the *p*H of the latter being measured with a glass electrode when voided. Four patients received quinacrine, five chloroquine and one santoquine. Alkali caused retention of these drugs and ammonium chloride gave rise to increased renal output. The magnitude of the changes in urinary excretion in the case of quinacrine was not correlated with similar changes in plasma levels since the excretion of this drug was low relative to dosage. There was a correlation in the case of the other two drugs and especially santoquine on constant oral dosage, since their rate of excretion was normally high, and alkalinization raised the plasma level while acid lowered it. The authors believe that renal excretion of these drugs depends to some extent on the plasma level obtaining at the time, but a number of other important variables are also involved and renal excretion cannot be used as an approximation method of indicating drug levels in plasma. They consider that the excretion of ammonia and weak organic bases in the urine are governed by *p*H changes in the latter. Other factors involved in renal excretion are discussed. An observation of clinical interest is that ammonium chloride could be of value when antimalarial drugs were giving rise to toxic symptoms because of the increased excretion caused, provided that the drug was normally excreted in large percentage in the urine.

[It is of interest in connexion with this investigation that ACTON & CHOPRA and also SINTON (this *Bulletin*, 1925, v. 22, 814 ; 1931, v. 28, 596) recommended the administration of alkali with quinine to render the drug more effective.]

J. D. Fulton

CARLSON, W. W. & CRETCHER, L. H. **The Hydroxyethyl Analog of Quinacrine.** *J. Amer. Chem. Soc.* 1948, Feb., v. 70, No. 2, 597–9.

DOBSON, J., HUTCHISON, W. C. & KERMACK, W. O. **Attempts to find New Antimalarials. Part XXVII. Derivatives of various Benzacridines and Pyridoacridines.** *J. Chem. Soc.* 1948, Feb., 123–6.

MONK, J. F. **Results of an Investigation of the Therapeutic Action of Paludrine and Pamaquin on Acute Attacks of Benign Tertian Malaria.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 657–62.

The patients treated were all soldiers returned to England from either India, Assam, Burma or the Malay Peninsula. One-third of the men were suffering from relapsing *P. vivax* infections ; the remainder were suffering from primary attacks. Patients who had had antimalaria treatment during the previous two weeks were excluded from the investigation. One hundred and seventy-nine patients were treated with paludrine 250 mgm. and pamaquin 10 mgm. every 8 hours for 10 days ; as controls 168 patients were treated with quinine 10 grains and pamaquin 10 mgm. every 8 hours for 10 days. Paludrine and pamaquin were given in tablet form, quinine in solution. The duration of fever after the commencement of treatment was significantly shorter in patients receiving quinine, 1·44 as compared with 2·1 days in the paludrine group. The persistence of parasitaemia was somewhat longer in the paludrine series, 1·85 days as compared with 1·5 days in the quinine group. The relapse rates of both groups during six months following treatment were almost identical, about 20 per cent. This relapse rate is much lower than that which follows treatment with either paludrine or pamaquin alone.

Thirty-seven per cent. of patients treated with paludrine and pamaquin had toxic reactions which included cyanosis, anorexia and gastric discomfort. Their clinical condition during treatment compared unfavourably with those treated with quinine and pamaquin, only 7 per cent. of whom showed any toxic symptoms. The dosage of 250 mgm. of paludrine every 8 hours is evidently too high when given concurrently with 10 mgm. of pamaquin; considerably lower doses give equally successful results. *Norman White*

MONK, J. F. **Results of an Investigation of the Therapeutic Action of Pentaquin on Acute Attacks of Benign Tertian Malaria.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 663–8, 1 graph.

Pentaquin is an 8-aminoquinoline derivative (6-methoxy-8-(5-isopropyl-aminoamylamino)-quinoline); it is closely allied to pamaquin and was synthesized in the U.S.A.

The patients treated were soldiers returned from the East. All had at some time taken suppressive mepacrine, but had ceased taking suppressive drugs on landing in England 4 to 5 weeks before developing symptoms of an attack of *P. vivax* malaria. Half these attacks were primary.

Twenty-five patients were treated with pentaquin 20 mgm. every 8 hours for 10 days. Twenty-six others received 10 grains of quinine concurrently with each dose of pentaquin. Clinical cure was rapid and compared favourably with that obtained by any other form of treatment. Half the patients exhibited toxic reactions, cyanosis, nausea, epigastric pain and flatulence. It appears that 60 mgm. a day is too high a dose for routine treatment.

The relapse rates during six months following treatment were only 12 per cent. in the pentaquin group and 11·5 per cent. in the pentaquin and quinine group.

Pentaquin reaches a stable level in the plasma as early as the third day, much earlier than does pamaquin. In one case detectable amounts were found in the blood 4 days after the last dose had been given, and in a large proportion of cases after 48 hours. Significant amounts of pamaquin are rarely found in the blood after 36 hours from discontinuing treatment. *Norman White*

FIELD, J. W., JOHNSTON, R. S. & SMITH, H. **Failure of Neo-Arsphenamine in Relapsing Vivax Malaria.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 677–8, 1 fig.

When the Changi internment camp, Singapore, moved to huts in open country in May 1944, *P. vivax* malaria appeared within a fortnight among a population of some 3,000 hitherto almost malaria-free. Within a few months there were over 500 cases, with frequent relapses controlled only by such limited suppressive therapy as could be provided. There was enough quinine, but little else: but as a small supply of neoarsphenamine was found in an Australian dump, it was given to twenty of the most seriously relapsing cases as follows:—

Quinine 1·0 gramme	Quinine 1·0 gramme	N.A.B. 0·45 gramme	—	—	—	—	—	—	—	N.A.B. 0·45 gramme
0	1	2	3	4	5	6	7	8	9	10

Day after relapse.

The patients were observed constantly until September 1945, with microscopic control. The chances of fresh infection at the time when injections began and afterwards were small: it was estimated that the chance of re-infection in any month ranged from 1 to 85 to 1 in 1,500.

The later history of the 20 patients is shown in a figure, which reveals that 19 of the infectious "held their own with scarcely a ripple in the relapse rhythm", which continued unchecked.

Referring to the very large numbers of cases of relapsing *P. vivax* malaria which will be seen in Britain and America for the next few years, and which will be given varied forms of treatment, the authors "trust that the fortune of those who pin their faith on neo-arsphenamine will be better than ours".

H. J. O'D. Burke-Gaffney

JANG, C. S., FU, F. Y., HUANG, K. C. & WANG, C. Y. **Pharmacology of Ch'ang Shan (*Dichroa febrifuga*), a Chinese Antimalarial Herb.** [Correspondence.] *Nature.* 1948, Mar. 13, 400–401.

A number of papers have recently appeared [this *Bulletin*, 1946, v. 43, 1012; 1947, v. 44, 699, 964] dealing with the antimalarial action and chemical nature of the substances present in the herb (*Dichroa febrifuga*) which has been used in the treatment of malarial fevers in China for centuries. Extracts of the roots (Ch'ang Shan) and more especially of the leaves (Shun Chi) have been found by the present authors to be active in *P. gallinaceum* infections of chickens. In all, 5 alkaloids, dichroine α, β and γ (which are quinazoline derivatives), dichroidine and quinazolone and two neutral substances, dichrin A (4-hydroxycoumarin) and dichrin B, have been obtained from the roots. The first three alkaloids are isomers and are mutually convertible under appropriate conditions. With the probable exception of dichroine α all the isolated substances are stated to possess activity against *P. gallinaceum*. Some chemical and pharmacological properties of the seven substances are given in a table which, however, is not very informative. Marked activity in *P. gallinaceum* infections has also been observed in an alkaloidal fraction from another Chinese herb Tou Ch'ang Shan (*Hydrangea umbellata*?) which is related to *Dichroa febrifuga* and from it the authors have succeeded in isolating several alkaloids.

In an added note, Dr. T. S. Work briefly comments on the chemical aspects of the problem.

J. D. Fulton

HENRY, A. F. X. Prémunothérapie catalytique du paludisme subaigu et du paludisme chronique. (Hémochromatophénolthérapie). [**Catalytic Premunition in Subacute and Acute Malaria (Haemochromatophenol Therapy).**] *Cahiers Méd. Union Française.* Algiers. 1947, Dec., v. 2, No. 15, 719–25.

SHUTE, P. G. & MARYON, M. **The Gametocytocidal Action of Paludrine upon Infections of *Plasmodium falciparum*.** *Parasitology.* 1948, Feb., v. 38, No. 4, 264–70.

The authors summarize the action of the older anti-malarial drugs on the gametocytes (crescents) of *Plasmodium falciparum* as follows:—

Quinine		
Heavy doses	During 1st or 2nd day ...	Crescents much reduced
30 grains daily	Later in attack	Crescents unaffected
Very small doses ...	Throughout	Crescents numerous
Sulphamethazine		
10 gm.	During 1st day of fever	Crescents very numerous
Mepacrine		
Very small doses ...	During 2nd and 3rd days	Crescents numerous
Larger doses	do. do.	Crescents less numerous
0·6–0·8 gm.	6th or 7th day	Crescents numerous
Plasmoquine		
Very small doses ...	Any time	Crescents sterile

They then report the results of a number of experiments with paludrine. A patient was infected with the Rumanian strain of *P. falciparum*. The primary attack and the first two relapses [= recrudescences] were lightly treated with paludrine or quinine. The third relapse was allowed to proceed unchecked and it produced a good crop of gametocytes, which readily infected a control batch of mosquitoes—*Anopheles maculipennis* var. *atroparvus* (87·5 per cent. positive). Paludrine was then given in two divided doses of 0·4 gm. each and batches of mosquitoes were fed daily on the patient for 8 days after the administration of the drug and again on the 12th day. Samples of mosquitoes were dissected at appropriate intervals and the results indicated that up to and including the seventh day after paludrine, the mosquitoes failed to become infective—thus confirming Fairley's work at Cairns [this *Bulletin*, 1946, v. 43, 527].

Exflagellation of the male crescent occurred normally, and oökinetes were plentiful in all the experiments, and the first indication that paludrine was having an adverse effect, was the small number of oöcysts appearing on the wall of the mid gut. The authors suggest that it is the females upon which the drug acts, without however giving any very satisfactory proof.

[The planning of this experiment is perhaps not quite satisfactory, as the control only refers to the conditions prevailing at the very beginning of the "crescent wave". It is important to view all work relating to the sexual phase of *P. falciparum* against the highly characteristic background of this phenomenon—as described for instance by the reviewer (this *Bulletin*, 1931, v. 28, 995).] *P. C. C. Garnham*

FARRELL, E. **The *Anopheles gambiae* Problem in Brazil and West Africa, 1941–44.** *Bull. U.S. Army Med. Dept.* 1948, Feb., v. 8, No. 2, 110–24, 11 figs. [Refs. in footnotes.]

Following the "unparalleled disaster" for the inhabitants of certain of the north-eastern states of Brazil because of *gambiae*-transmitted malaria, the joint efforts of the Rockefeller Foundation and the Brazilian Government had by 1940 eradicated *A. gambiae* from Brazil, "one of the finest public health achievements of the age." During the recent war, Brazil lay astride the heavily used airborne traffic routes from the U.S.A. and the Caribbean to the Mediterranean and Middle East Theatres of War *via* Senegal or Liberia or the Gold Coast.

The introduction of *A. gambiae* by air traffic to Brazil and the Caribbean was therefore an ever-present possibility. Indeed, with increase in this traffic, the Brazilian Port Health Service became increasingly alarmed at the numbers of *A. gambiae* found in aircraft arriving from Africa. Despite heavy penalties, the ordinance—which required incoming pilots to keep canopies down and cabin windows closed until the plane had been sprayed by Brazilian staff—was not completely effective; the escape of a single gravid female *A. gambiae* to areas beyond the controlled precincts of the airport might well mean disaster for Brazil.

Numbers of *A. gambiae* reaching Brazil became so alarming that the Brazilian Government, through both military and diplomatic channels, made representations to the Secretary of State, U.S.A. As a result, the U.S. War Department took special action and sent a small expert Commission to investigate the situation. This Commission reported in December 1943, that "the cause of Brazil's *gambiae* problem lay not so much in neglect of current aircraft spraying regulations as in the neglect of environmental sanitation at West African airfields of departure, where *gambiae* mosquitoes were breeding in large numbers in the immediate vicinity of aircraft parked overnight prior to take-off for

Brazil." The Commission felt that "the sanitary frontier of the New World lay overseas and *A. gambiae* had to be beaten on its own ground in the ruts and water holes of the West African airfields and their adjacent terrain." The creation of a single anti-*gambiae* organization in West Africa was recommended, the objective being "the rendition of West African airfields *gambiae*-free." Such an effort was also justified by the "extraordinary" prevalence of malaria among American personnel in West Africa. By March 1944, 16 officers and 90 enlisted men were engaged in co-ordinated mosquito control activities at American Army posts in Nigeria, Gold Coast, Senegal and Liberia; a malariologist was in control of this organization.

The U.S. Army took over control of Accra Air Base on October 1st 1942; previously Pan American Airways, Africa, Ltd. had depended for malaria control primarily on the application of individual preventive measures, such as screening, housing, repellents and suppressive medication, and with a fair measure of success, but not to the degree suggested by incidence rates. These figures rather misled U.S. Army authorities when they took over Accra and other posts, with the result that few effective measures were taken and a high incidence of malaria ensued in 1943. The activities of the specialist malaria staff in 1944 had the expected results in Nigeria, Gold Coast and Senegal but not in Liberia, where anti-mosquito measures had to be confined to areas within a mile radius of the installation.

Monthly malaria rates (cases/1,000/annum) are tabulated as follows:—

I 1941–1942. British Army and Pan American Airways, Accra, Gold Coast.
II 1943–1944. British Army, U.S. Army, R.A.F., Accra, Gold Coast.
III 1943–1944. U.S. Army, according to Locality, West Africa.

[The headings of Tables I and II "—personnel stationed at Accra, Gold Coast and British West Africa" are misleading and in fact, appear to refer to Accra airfield and vicinity only and not to all military or air installations in West Africa.]

The following extract from Table III quotes the figures of high and low monthly incidence for 1943 with the comparative figures for 1944:—

	Cases/1,000/annum							
	Nigeria		Gold Coast		Liberia		Senegal	
	1943	1944	1943	1944	1943	1944	1943	1944
Month of high incidence	1,314	446	897	683	1,068	1,686	1,952	64*
Month of low incidence	150	22	164	258	492	663	168	107
*October, 1944		45		34		157		64

*Quinacrine suppressive medication was introduced in August 1944.

It is concluded that the general reduction in malaria incidence can be attributed to the anti-*gambiae* programme, which included species eradication measures. Collaboration with French and British services particularly in Accra contributed to the success attained; in the latter instance an Inter-Allied Malaria Control Scheme [the officer in charge was a member of a British Malaria Field Laboratory] envisaged permanent control over mosquito breeding in a large area through an extensive system of permanent drainage ditches.

[In support of his conclusions of the effectiveness of environmental control over *gambiae* breeding, the author provides a chart for 1944 in which are compounded the weekly malaria rates and rainfall for all U.S. Army installations in West Africa, with superimposed adult mosquito densities. To the reviewer

such a summary is misleading as the localities concerned vary so much in quantity of rainfall and other climatic conditions; moreover in the text the author refers to this chart to illustrate conditions in one place, Accra; the inference is that an error has occurred in the legend to this chart and that "West Africa" should read "Accra, West Africa."]

Across the Atlantic, the Director of the Brazilian Port Health Service expressed complete satisfaction with conditions achieved at Accra and Dakar by July 1944.

[This paper serves to emphasize once again the unreliability of insecticide measures in aircraft as the sole means of prevention of transfer of mosquitoes from one territory to another.] *R. Ford Tredre*

DEONIER, C. C., FLUNO, J. A. & NOTTINGHAM, E. **Preflooding Treatments with DDT for Mosquito Control.** *Science.* 1948, Jan. 16, 63–4.

The residual toxicity of DDT has suggested the possibility of spraying mosquito breeding grounds before they become flooded and infested with the larvae. Preliminary results on a field scale have been good in several cases, but poor in others.

Some laboratory tests were done to ascertain which type of carrier was likely to give best results. The mosquitoes used in repeated tests were *A. quadrimaculatus*, *Aëdes aegypti*, and *C. quinquefasciatus* [*fatigans*]. One series of tests was done in jars with mud ("muck") bottoms and the other with sand at the bottom. Treatments were applied with water present (to even out distribution), the water was dried out and more water added ("flooding"). Mosquito larvae were introduced and examined for mortality later. The first "flooding" was done three weeks after application and the water was dried out after the test and the process repeated after eight and twelve weeks. The DDT was applied at the rate of 0·2 lb. per acre as a kerosene solution, an emulsion, a suspension or as a dust.

The mortality decreased with successive floodings, the emulsion treatment having poorest lasting qualities. At the final test, the DDT suspension series gave highest kill of *A. quadrimaculatus* and the DDT dust was the most effective residue for *Aëdes aegypti*. (The kerosene solution was not far behind.) In all dishes except those treated with emulsion, the residual effect was greater with sand than with a mud bottom.

A field test with 10 per cent. DDT dust applied at 1 lb. of DDT per acre before flooding gave very good results in suppression of larval development.

J. R. Busvine

SIMMONS, S. W., FERGUSON, F. F. & UPHOLT, W. M. **Larviciding for the Control of Malaria Mosquitoes.** *Mosquito News.* 1947, Dec., v. 7, No. 4, 139–44.

DDT dusts, smokes, bombs, candles and emulsions are briefly discussed and compared with an oil-spray technique which is described in some detail.

Laboratory tests showed that oil sprays containing DDT applied at the rate of one part DDT per one hundred million parts of water killed over 50 per cent. insectary-reared anopheline larvae in 24 hours. In the field, the application of one gallon of fuel oil with 0·05 pound of DDT per acre of water surface has resulted in over 90 per cent. kill of all instars of larvae. The hand technique involves the use of a small (1½ to 4 gallons) air pressure sprayer with a suitable nozzle to atomize the DDT oil solution. Pressure should be kept up to between 30 and 50 pounds per square inch. The operating technique is described; and as the DDT kills first stage larvae as well as the later stages, there is considerable saving in labour, material and in time, one trip often sufficing when two trips

would be necessary with simple oil larvicides. As against this, the method requires better trained control men, is dependent on the type of breeze, and the treatment has little effect on pupae.

Details are also given of the equipment and method of application of the DDT-oil spray technique from aeroplanes. *H. S. Leeson*

HINMAN, E. H. **Recent Trends in Malaria Control in Latin America.** *Mosquito News.* 1947, Dec., v. 7, No. 4, 144–51. [12 refs.]

PARAENSE, W. L. Estudos sôbre o ciclo exoeritrocitario do *Plasmodium gallinaceum.* [**Exoerythrocytic Cycle of** *P. gallinaceum.*] *Mem. Inst. Oswaldo Cruz.* 1947, Mar., v. 45, No. 1, 101–18. [13 refs.]

A general discussion on the development of exoerythrocytic forms of *P. gallinaceum* following blood and sporozoite inoculations, and the influence of quinine in suppressing the blood infection and permitting the development of fatal exoerythrocytic infection [this *Bulletin*, 1948, v. 45, p. 47].

C. M. Wenyon

LEWERT, R. M. **Alterations in the Development of** *Plasmodium gallinaceum* **following Passage through Tissue Culture.** *Science.* 1948, Mar. 5, 250.

Plasmodium gallinaceum was grown in tissue culture according to the technique of GEY and GEY (*Amer. J. Cancer*, 1936, v. 27, 1), the culture being started either from infected pia mater or from heart muscle. Extensive development did not occur, but growth of the parasite continued for as long as 70 days after several subcultures. However, the interesting part of this work lies in the result of the inoculation of these cultures into chicks 7–32 days old. The chicks invariably developed an infection of an exclusively exoerythrocytic nature and overwhelming in intensity. No pigmented parasites were ever seen, though in several instances a low percentage of the erythrocytes contained minute uninuclear forms. This peculiar type of infection was maintained unchanged through 9 passages, when intraperitoneal subinoculations of brain emulsions were employed. When blood instead of brain was subinoculated from the same series of chicks, pigmented erythrocytic parasites reappeared by the third passage, though even as late as the eighth, the infection continued to be preponderantly exoerythrocytic. It may be noted that by the employment of this technique, parasites as young as four days can readily be found in the capillary endothelium of the brain. *P. C. C. Garnham*

ERRATUM

In the abstract of the papers by SHORTT *et al.*, this *Bulletin*, 1948, v. 45, 388, the reference to HUFF & COULSTON in line 4 should read (*J. Parasitology*, 1947, v. 33, No. 6, Sect. 2 (Supp.), 27). An abstract of this paper will appear in the September number of this *Bulletin*.

BLACKWATER FEVER

LIMBOS, P. A propos d'un cas de fièvre bilieuse hémoglobinurique chez un enfant indigène. [**A Case of Blackwater Fever in an African Infant.**] *Ann. Soc. Belge de Méd. Trop.* 1947, Sept. 30, v. 27, No. 3, 285–8.

The author describes a case of blackwater fever which occurred during an acute attack of *P. falciparum* malaria in an African child of 23 months in the Belgian Congo. The haemoglobinuria appeared a few hours after an injection of 0·5 gm. of quinine. The patient had had several previous attacks of malaria and was given quinine, prophylactically and curatively, at frequent but irregular intervals by his father, despite medical advice to the contrary.

After the attack of blackwater fever had been cured by general measures and the existing *P. falciparum* infection had been treated with mepacrine, the patient, five days later, developed another acute attack of malaria, with *P. falciparum* in his blood. He suffered from four more such attacks within the following year. Because of the ever-present danger of blackwater fever in a susceptible subject, it was decided to try the effect of mepacrine prophylaxis. The last attack was treated, like its predecessors, with 0·1 gm. of mepacrine, daily for 5 days, followed by 0·01 gm. of plasmoquine daily for 5 days : afterwards, 0·1 gm. of mepacrine was given under direct medical or nursing supervision every Monday and Thursday. No more malarial attacks have occurred, the blood has remained negative on five examinations, and the spleen is not palpable. The child attends the dispensary regularly twice a week for mepacrine prophylaxis and is in excellent health at the present age of 3 years and nine months. The author reaffirms the danger of irregular quinine prophylaxis in Africans and the indiscriminate use of the drug without medical control.

The rarity of blackwater fever in Africans owing to the "premunition" established is well recognized ; it is suggested that this exceptional case occurred because the patient's circumstances regarding frequent malarial attacks and the irregular taking of quinine were the same as those commonly encountered among Europeans who develop blackwater fever. *H. J. O'D. Burke-Gaffney*

LASER, H. **Haemolytic System in the Blood of Malaria-Infected Monkeys.** [Correspondence.] *Nature.* 1948, Apr. 10, 560.

This is a preliminary report, details of which will appear elsewhere, of a haemolytic substance found in heavily parasitized (*Plasmodium knowlesi*) monkey blood : the parasites seem to produce it or cause its appearance in the erythrocytes, which it destroys when its concentration is high ; it is then released into the plasma. It does not appear to differ (except in its higher quantity) from a haemolytic substance obtained from normal blood and other tissues, and previously reported by the author and FRIEDMANN (*Nature*, 1945, Oct. 27, 507). It has so far been characterized as an unsaturated monocarboxylic fatty acid having one double bond and the possible chain-length C18. Its haemolytic activity is inhibited specifically by antimalarial drugs.

The mechanism may be thought of as enabling the metabolic utilization of the red cell by the parasite. Malaria pigment, which is a haematin compound, accentuates this mode of erythrocytic destruction by the parasite : haematin has itself been found to be haemolytic *in vitro* in low concentrations and in sub-haemolytic concentrations it strongly potentiates the effect of the haemolytic substance now described.

The author notes that it might be interesting to study the quantitative relations of these two factors in the blood of persons suffering from blackwater fever. *H. J. O'D. Burke-Gaffney*

TRYPANOSOMIASIS

LOURENÇO MARQUES. Conferência Intercolonial sobre Tripanossomíases, Lourenço Marques, 26 a 31 de Agosto de 1946. [**Inter-Colonial Conference on Trypanosomiasis, Lourenço-Marques, 1946.**] Vol. I. 387 pp. Vol. II. 458 pp. Numerous figs., maps & charts. 1947. Lourenço Marques: Imprensa Nacional de Moçambique.

It is evident that the Conference which took place in Portuguese East Africa on trypanosomiasis in 1946 was important. It was attended by delegates from almost all parts of British and Portuguese Africa, in which tsetse occurs, and among them there were men interested in human and animal medicine, entomology, agriculture and administration.

The report of the Conference is in English and Portuguese, and every word, including small parts of the discussion, is set down in both languages. The report has, therefore, a tendency to be diffuse and it is not easy to extract the conclusions or to find which parts of it are of permanent value. Certain topics which were discussed more than once appear in several different places; the table of contents is so brief that it does not give one much help.

Where Portuguese originals have been translated into English the language is generally good and clear. A few technical errors have been noted, for instance "ape" for "baboon", "Iorke" for "Yorke" and "oxen plague" for "rinderpest". The phrase "typical podagral lesions were found in cudos" is presumed to mean that foot lesions, characteristic of foot and mouth disease, were found in kudus.

The report is illustrated with numerous maps, many of them in colours, and with half-tone blocks of the delegates sitting at the conference. The general presentation of the report reflects great credit on the Government printer at Lourenço Marques.

The volumes contain valuable information on several sides of the subject which had previously been obscure. The coloured maps give the distribution of *Glossina* as a whole and of some of the species, also distribution of trypanosomiasis of man and animals. Some of them deal with parts of the world such as Angola, Swaziland and Portuguese East Africa, about which it has been difficult to get up-to-date information. We note also a report by HORNBY on the present distribution of *G. morsitans* along the Save River and on the possible danger of its extension to the lower part of the valley of the Limpopo.

There are two valuable contributions from CHORLEY of Southern Rhodesia. In the first he deals with the history of the distribution of *G. morsitans* and nagana in that territory, much of his facts being gathered from the records of hunters and travellers about seventy to ninety years ago. It is evident that fly was driven back, probably because hunters and the great epidemic of rinderpest in 1896 killed the game. The fly then commenced to re-occupy much territory. The second paper gives a general account of the measures, principally game exclusion and game destruction, which were undertaken to drive *G. morsitans* back again. This is a very important piece of work, for Southern Rhodesia has recovered a much larger area from fly than has any other African territory. The present paper is the only general account of what has been done, and we feel that the matter deserves more than the three pages given to it. We understand that the cost of the operation was remarkably low, but on that no information is given.

South African authors gave the conference an account of the use of DDT in mineral oil sprayed from the air against *G. pallidipes* in a small game reserve in Zululand. The paper by DU TOIT gives most useful information on the practical measures undertaken, *e.g.* organization, spray formula, dosage, cost and the effect on the tsetse as measured by traps.

It is evident that the clinicians had a varied and stimulating day. Sousa Santos first discussed what criteria should be used in estimating a cure of Gambian sleeping sickness; Ramos and Assoreira passed on to consider blindness in this infection: it is attributable to "trypanosomic opto-chiasmatic arachnoiditis". This condition is apparently to be treated by intracarotid injections of tryparsamide, peri-carotidal sympathectomy, or even frontal craniotomy to eliminate adhesions in the opto-chiasmatic region. Penicillin when administered by the intravenous or intramuscular route is without effect on trypanosomiasis. If it is given intrathecally, the trypanosomes disappear temporarily from the cerebrospinal fluid but the course of the disease is not affected.

The report contains much else that is valuable, *e.g.* a discussion on the relation of tsetse problems to game and to afforestation, and a terse account by Potts of the relation between fly and vegetation.

The formal recommendations of the conference appear to have been written in a conservative and somewhat platitudinous mood. Among the more interesting ones, there is a proposal for the rapid exchange of information between territories, both on the distribution of tsetse and trypanosomiasis and on the progress of measures of control. A list of Government organizations which should be kept informed has been drawn up, and the Government of the Colony of Mozambique is invited to approach the French and Belgian authorities asking them to participate in the exchange of information. It is also desirable that bibliographies and summaries of work published should be circulated. [It does not appear to have been pointed out at the conference that some of these functions have been carried out not unsuccessfully by the *Tropical Diseases Bulletin* and its predecessor the *Sleeping Sickness Bulletin*, since the year 1908.] There are also proposals for the use of uniform symbols in mapping the distribution of tsetse and trypanosomiasis: such symbols are illustrated at the end of the Report. *P. A. Buxton*

Sandground, J. H., with the technical aid of Rosey Maynard. **Experimental Studies of an Old Strain of *Trypanosoma gambiense*. I. The Enhancement of its Virulence and the relationship of this Phenomenon to the Species of Polymorphic Trypanosomes of Africa.** *Ann. Trop. Med. & Parasit.* 1947, Dec., v. 41, Nos. 3/4, 293–305, 2 figs. on 1 pl. [27 refs.]

While the trypanosomes of the *brucei* group are morphologically indistinguishable and therefore constitute only a single species, on clinical and epidemiological grounds they are referable to distinct categories, corresponding to *T. gambiense*, *T. rhodesiense* and *T. brucei*. The first two parasites differ not only in the degree of pathogenicity to man but also in their response to treatment with drugs and in virulence to laboratory rodents. In the last respect *T. rhodesiense* resembles *T. brucei* more closely than it resembles *T. gambiense*.

In the present paper, an account is given of the experimental transformation of a typical *T. gambiense* into a strain highly pathogenic for laboratory rodents. The original "Nzale" strain was brought to the United States from the Belgian Congo, where it was isolated from a wild *Glossina palpalis* into a guineapig, and passed through other guineapigs, as well as through man. Using a "standard infection", produced by intraperitoneal inoculation of blood containing one million trypanosomes, the author studied the behaviour of "Nzale" strain in laboratory rodents. The infection in guineapigs was symptomless with an average duration of 78 days. In rabbits, mice and hamsters its course was even more benign, usually terminating in spontaneous recovery, with trypanosomes rarely appearing in the blood. Adolescent rats (35–50 days

old) rarely showed signs of infection, while trypanosomes were present in the blood in varying numbers, the average survival time of these animals being 166 days.

Since such benign infections in rodents were unsuitable for chemotherapeutic tests, it was decided to increase the virulence of this strain. Whereas rapid syringe-passages through rodents, splenectomy and blockade of the reticulo-endothelial system, failed to produce the desired effect, success was obtained by inoculation of nursling rats, 17 days old, with a heavy suspension of trypanosomes from an adult rat. Some of the young rats were heavily infected after 3 days, their average survival time being 32 days. Further passages through young rats brought about a gradual increase in the virulence until the 7th serial passage, when the duration of the infection was reduced to three days. Infection of older rats with the modified strain, described as "V", resulted in their death after 4 days, while the original "Nzale" strain retained its non-pathogenic character throughout the experiments. The behaviour of "Nzale" and "V" strains in rodents was compared in parallel experiments. In mice infected with "V" strain, there was progressive parasitaemia terminating in the death of the animals by the 5th day, while those infected with "Nzale" strain showed scanty trypanosomes or none at all and the majority of the animals survived. All rats infected with "V" strain died within 7 days, while those infected with "Nzale" had scanty infections and died at irregular periods between the 25th and 95th days of infection. The average survival time of hamsters infected with "V" strain was 16·8 days; these animals also showed evidence of involvement of the central nervous system. On the other hand, the "Nzale" strain produced no visible signs of infection in hamsters. In contrast to the avirulent effect of "Nzale" strain, "V" strain killed rabbits within 60 days, with symptoms of acute disease, manifested by lymphadenopathy and atrophy of cardiac muscles. In guineapigs the contrast between the two strains is less marked.

In addition to enhanced virulence, the "V" strain of *T. gambiense* revealed changes in susceptibility to drugs and in general behaviour, which were indistinguishable from those of a strain of *T. brucei* studied in the same laboratory. Like *T. brucei*, it is sensitive to antrypol (Bayer 205) and to stilbamidine, but is not affected by the highest tolerated doses of tryparsamide.

The stability of strain "V" was demonstrated by failure to produce its attenuation after inoculation of small doses of trypanosomes into adult rats and after passages through various other rodents. On the other hand, the experiment of enhancing the virulence of "Nzale" strain by inoculation of young rats was successfully repeated several times.

In conclusion, the author discusses the bearing of his experiments on the question regarding the phylogenetic relations of trypanosomes of the *brucei* group. Since in these experiments "by controlled and reproducible laboratory procedures, a typically *gambiense* trypanosome has been modified to produce a strain characteristic in every way of *T. brucei* or of *T. rhodesiense*", it is held that similar changes might occur under natural conditions. Furthermore, the present findings seem to indicate that the age of the host might be "a potent element in favouring the enhancement of virulence among trypanosomes." Consequently "infection of very young hosts may represent the means whereby virulent strains of the human trypanosomes of West Africa are produced in nature."

The author regards *T. gambiense* and *T. rhodesiense* as "mutant variants of a single species which the international zoological laws of nomenclature would by reason of priority recognize as *T. brucei*". [This view was previously expressed by the reviewer: see this *Bulletin*, 1944, v. 41, 150.]

C. A. Hoare

BESSEMANS, A., WITTEBOLLE, P. & BAERT, H., Mlle. Etude, par la micromanipulation, de la virulence d'un ou de plusiers trypanosomes et de granules de sang trypanosé. [**A Study by Micromanipulation of the Virulence of Single or Several Trypanosomes and of Granules in the Associated Blood.**] *Rev. Belge Sci. Méd.* 1946, Oct., v. 17, No. 5, 284–9. [29 refs.]

A review is given of previous attempts to infect animals by few or single trypanosomes. Infections produced by single trypanosomes have been reported by various workers during the past thirty years. The present work was carried out with an arsenic-resistant stain of *T. gambiense*, with a normal strain of *T. gambiense* and with a Belgian strain of *T. equiperdum*. By means of a micromanipulator, trypanosomes were isolated from citrated blood and injected subcutaneously into other animals. Eight guineapigs were inoculated with 1 to 20 trypanosomes from the arsenic-resistant strain of *T. gambiense*; no infections resulted. Similarly, nine other guineapigs were inoculated with one to fifty parasites from the ordinary strain of *T. gambiense*; none became infected. With the strain of *T. equiperdum*, transmission to mice was achieved in one of 36 animals inoculated with a single trypanosome. With 2–5 trypanosomes, about 8 per cent. of a limited number of animals became infected. But even with as many as 50 to 200 trypanosomes, failure to infect often occurred. Twenty mice were inoculated with the granules which occur in the blood of animals with trypanosomiasis. None of these animals became infected. In other experiments the blood taken from guineapigs during the lytic stages of the infection was not infective for mice although apparently it contained many trypanosomes. *F. Hawking*

MORACZEWSKI, S. A. & KELSEY, F. E. **Distribution and Rate of Metabolism of Phosphorus Compounds in** *Trypanosoma equiperdum*. *J. Infect. Dis.* 1948, Jan.–Feb., v. 82, No. 1, 45–51, 1 fig. [15 refs.]

A study has been made of the phosphorus metabolism of *T. equiperdum in vitro* and *in vivo*, with the aid of P^{32}, a radioactive isotope of the element. In the *in vitro* investigations, trypanosomes were isolated by centrifugation from the blood of infected rats and were then suspended in a saline-phosphate medium containing 2 per cent. protein at *p*H 7·6 to 7·8 and maintained at 37·5°C. The motility of the trypanosomes was impaired by repeated washing and their total phosphorus content was reduced.

In experiments with radioactive phosphorus, the labelled element with an activity of 3 millicuries per mgm. was added to the medium as phosphate, to give a concentration of 0·5 mgm. phosphorus per cc. Total phosphorus was measured by chemical methods and radioactivity by means of a Geiger-Müller counter. A method based on that of SCHNEIDER (*J. Biol. Chem.*, 1945, v. 161, 293) was used on aliquots of trypanosome suspensions to estimate the distribution of phosphorus in the acid-soluble, phospholipid, nucleic acid, and phosphoprotein fractions. In the *in vivo* experiments in which 10 mgm. of labelled phosphorus, as neutral phosphate containing 20 millicuries of P^{32}, was given intraperitoneally to rats, phosphorus was similarly estimated in the four different fractions of isolated trypanosomes, in plasma and in homogenates of heart and liver. In view of the results of CHEN & GEILING (*Proc. Soc. Exper. Biol. & Med.*, 1946, v. 63, 486) who showed that a phosphorylating mechanism was concerned in the breakdown of glucose to pyruvic acid, the authors believe that the acid-soluble fraction may contain the phosphorus compounds involved in this process. While the total P present in trypanosomes kept in presence of stable or radioactive phosphorus was similar, the distribution in the various

fractions was altered, as a result, the authors believe, of the greater concentration of phosphorus in the medium made necessary for the measurement of radioactivity. During *in vitro* experiments the trypanosomes became less active and probably more permeable, thus vitiating to some extent the measurement of phosphorus exchanges which the authors considered to be of negligible proportions. The exchanges in three of the fractions *in vivo* were very much greater than those *in vitro* when measured after injection of the infected animal with labelled phosphorus. The turnover was in fact greater in the case of the trypanosomes than in the host tissues and showed that the parasites could utilize the inorganic phosphorus present in plasma for the synthesis of organic compounds of this element. *J. D. Fulton*

Spinks, A. **Persistence of Suramin Analogues in the Blood Stream.** *Biochem. J.* 1948, v. 42, No. 1, Proc. Biochem. Soc. vi.

Gage, J. C., Rose, F. L. & Scott, Mary M. **The Estimation of Suramin (Antrypol, Bayer 205) in Plasma.** *Biochem. J.* 1948, v. 42, No. 1, Proc. Biochem. Soc. vi.

Caldwell, A. G. & Walls, L. P. **Potential Trypanocides of the N-Heterocyclic Series. Part I. Phenanthridinium Salts.** *J. Chem. Soc.* 1948, Feb., 188–97.

Symes, C. B., Hadaway, A. B., Barlow, F. & Galley, W. **Field Experiments with DDT and Benzene Hexachloride against Tsetse** (*Glossina palpalis*). *Bull. Entom. Res.* 1948, Feb., v. 38, Pt. 4, 591–612, 4 maps, 3 text figs. & 3 figs. on 1 pl.

The five experiments described in this paper were performed in Uganda in 1946. Vegetation was sprayed with DDT and gammexane to a height of 6 feet. The first test took place on Nfo, an unoccupied island of 100 acres in Lake Victoria, about a mile from the mainland, where the tsetse population was estimated to be 11,700. Gammexane (0·65 per cent. gamma) in 50 per cent. kerosene and 50 per cent. cottonseed oil was applied by Four Oaks Kent sprayers at a rate of 2·2 quarts per 1,000 square feet. The selected patches amounted approximately to 2 acres. The fly reduction was estimated at 50 per cent. over a period of 10 days, after which the numbers began to increase. After 4 weeks they had reached pre-treatment numbers. The spraying was then repeated and some additional areas were included ; for a week afterwards the reduction in fly density was about 80 per cent., but rose again. Deposits of gammexane on leaf surfaces of samples of treated vegetation were low even one day after application.

Areas of vegetation on another island, Mbirubuziba, about a mile from the mainland, were similarly treated ; this time with DDT (5 per cent. in 50 per cent. kerosene and 50 per cent. cottonseed oil). About 1·7 acres of a total of 30 acres were treated. Reduction of fly was estimated at 80 per cent. for a week, then the numbers increased. There seemed to be an appreciable loss of insecticide through penetration of the leaves.

In a later test on the same island, four applications of DDT were made at intervals of 10 to 14 days. The selected areas of vegetation along the coast and in the centre of the island amounted to about 4 acres. From the 6th to the 13th week after the final application, no flies were seen or caught, then 2 flies were captured. Again there was considerable loss of insecticide from leaf surfaces, some of it through rain.

The last experiment was made at Nkumba, a peninsula of the mainland, where a linear distance of about 9,000 yards was treated. Four applications of DDT were made, the first two consisting of one part ATSO (DDT in naphtha,

used with an emulsifier) and two parts of lake water and the other two of 5 per cent. DDT in deiseline. The movement of cattle and rainfall interfered with the trial to some extent, and as a result of the rainfall the growth of the vegetation was very rapid. The fly density was reduced by about 98 per cent. but a week after the final application flies began to appear in fair numbers at some points. Insecticide deposits on sample papers and leaves were small, though the ATSO emulsion persisted for several weeks and gave fairly good kills. Deposits of 116 and 173 mgm. per square foot on leaves of *Dracaena* gave kills of 100 per cent. and 93 per cent. respectively for 8 and 16 weeks afterwards. Deposits on hairy leaves gave negligible kills.

The authors conclude that these rather laborious methods, even at excessive dosages, are not likely to eliminate *Glossina palpalis*. The experiments show that an insecticide is required that will not be absorbed by the vegetation, and that will not lose its toxicity, and a method will have to be devised that will give much greater coverage than can be achieved with small knapsack sprayers.

H. S. Leeson

Laranja, F. S., Dias, E. & Nobrega, G. O eletrocardiograma na cardiopatia crônica da doença de Chagas. [**The Electrocardiogram in Chronic Cases of Chagas's Disease.**] *Brasil-Medico*. 1948, Feb. 21 & 28, v. 62, Nos. 8/9, 51–2. English version 52–3.

This appears to be a summary of a paper presented to or read at an Inter-American Congress of Cardiology, held in Mexico in October 1946, and based on investigations carried out in Minas Gerais. The authors studied 357 cases of chronic Chagas's disease and electrocardiographic alterations were found in 208 (58·2 per cent.) of them. These included extrasystole of ventricular origin, A-V blockage of different types, intraventricular block, nearly always of the right branch bundle (90 out of 92) ; QRS changes with or without T-wave alterations ; P-wave alterations, usually transient, and, less commonly, auricular fibrillation. Arrhythmia was present in just over half (52·9 per cent.) of those with abnormal electrocardiogram, usually ventricular in origin, and the authors maintain that extrasystoles persisting after effort point strongly to cardiac involvement in patients with Chagas's disease. A-V block was observed in 21·5 per cent. of those showing ECG abnormalities and this is regarded as an early change ; so much so that when this symptom is found in patients under 40 years of age, other, confirmatory, signs of Chagas's disease should be looked for. Another peculiarity is the suddenness with which changes may occur in the A-V and intraventricular conduction time. Alterations of the T-wave might be temporary and transient or permanent, like those seen in ischaemia of the anterior wall (" coronary T-wave ") ; if the former, they would show progression and retrogression in cycles which varied in different patients. In ordinary cases of Chagas's disease auricular fibrillation is not common, but when present is of bad import, as Chagas himself noted ; if, however, it is associated with arteriosclerosis it may react to quinidine and the prognosis is more favourable. Only slight changes are frequent in the P-wave ; marked change is very rare [figures are not given].

H. Harold Scott

LEISHMANIASIS

Shi Lu Chang & Negherbon, W. O. **Studies on Hemoflagellates. III. The Specificity of Serological Reactions of** *Leishmania donovani*, *L. brasiliensis*, *L. tropica*, **and** *Trypanosoma cruzi*. *J. Infect. Dis.* 1947, Nov.–Dec., v. 81, No. 3, 209–27, 10 figs. on 2 pls. [17 refs.]

Employing the culture method described in an earlier paper [this *Bulletin*, 1947, v. 44, 1055] the authors have tested the serological reactions of two strains of *Leishmania donovani* and *Trypanosoma cruzi* and of one strain of *L. brasiliensis* and *L. tropica*. Guineapigs were immunized against *T. cruzi* by injecting them intraperitoneally with living organisms or with 0·5 to 2 cc. of the packed killed organisms, it being estimated that 1 cc. contained 2,500,000,000 flagellates. The organisms were killed with formalin which was added to the washed suspension of flagellates to give a concentration of 0·025 per cent., or by heat, an exposure to 50°–55°C. being given for 20 minutes. For the leishmania, only living organisms were used for immunization. Blood was taken from the guineapigs by heart puncture after the 6th, 8th and 13th injections of antigen given at intervals of three to four days. Agglutination tests were carried out with various dilutions of serum, the microslide test with living organisms giving the best results. In all cases, the sera gave a good agglutination with the homologous organism but a weaker agglutination was always given with the other organisms.

Furthermore, with increased dilution of the sera, the heterologous agglutination disappeared first, the homologous agglutination persisting at a – reaction with dilutions of 1 in 1,280 to 1 in 2,560. In the complement-fixation tests, both a glycerinated antigen and one prepared by lyophilizing thoroughly washed organisms suspended in normal saline were used. No significant difference in the potency of these antigens was noted. In the precipitation reaction the ring test was found to be the most delicate. The lytic effect of antisera at low dilutions could not be eliminated with the leishmania, but could be in the case of the more resistant *T. cruzi*. Absorption of antiserum with homologous antigen removed the species as well as the cross-reacting antibodies, while absorption of antiserum with heterologous antigen removed all of the respective antibody, part of the cross-reacting antibodies and reduced the agglutination titre against the homologous antigen organisms. Ghost-cells gave the same reactions as living cells, but a lower titre of the homologous antigen. The general result of the observations is that the culture forms of the organisms tested have both species-specific and common antigens and that the specific antigen is predominant while the common antigen is probably a combination of several antigen components. *C. M. Wenyon*

FEVERS OF THE TYPHUS GROUP

Revol, L., Coudert, J. & Morel, P. Etude de la moelle osseuse par ponction sternale de neuf cas de typhus exanthématique. [**Study of the Bone Marrow obtained by Sternal Puncture in Nine Cases of Exanthematic Typhus.**] *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 11 12, 479 82.

The authors give a brief summary of the scanty literature dealing with the changes found in the bone marrow in typhus fever, and then describe the conditions found in nine cases studied at the height of the attacks.

The chief findings were : (1) The haemocytoblasts were increased above the normal limits in six cases. (2) The neutrophile myelocytes were diminished in eight cases. (3) The eosinophile myelocytes were increased in six cases (4) The eosinophile polynuclears were increased in eight cases, and reached the upper limit in the ninth. (5) The proerythroblasts and basophile erythroblasts were increased in eight cases. *John W. D. Megaw*

Cotrufo, P. & Zito, P. Istopatologia dei vasi sanguigni nel dermotifo. [**Histopathology of the Small Blood Vessels in Typhus.**] *Acta Med. Italica.* 1948, Jan., v. 3, Supp. No. 1, 1–6, 7 figs. [43 refs.]

The English summary appended to the paper is as follows :—

" The authors have studied the vasal and reticulo-endothelial reaction in the cutis, lungs, spleen, liver and meninges during the evolution of typhus.

" The authors conclude that in the course of typhus are observed histologic alteration of the small vessels, consisting in processes of the necrotic degenerative type of the arteries and in processes of adventitial proliferation.

" In connection with the haemorrhagic manifestations, are seen special macrophage cells of the reticulo-endothelial system which englobe the haemoglobin residues."

Guerrisi, G. La glomerulonefrite nel dermotifo. Nota I. [**Glomerulonephritis in Typhus.**] *Acta Med. Italica.* 1948, Jan., v. 3, Supp. No. 1, 6–10, 4 figs.

The English summary appended to the paper is as follows :—

" During the course of typhus is noticed sometimes evidence of glomerulonephritis ; in its pathogenesis are often present oro-pharyngeal septic complications.

" The histologic observation shows that the glomerular alterations are mostly in connection with the alterations of the polar vessels and of the special structures involving them, which account for a particular activity regulating the vascular glomerular retis."

Badenski, G. & Drouhet, E. La réaction de fixation du complément dans 84 cas de typhus exanthématique épidémique, utilisant les rickettsies comme antigène. [**The Complement-Fixation Reaction in 84 Cases of Epidemic Typhus, with a Rickettsial Antigen.**] *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 11/12, 417–20.

In a series of comparative tests, the authors found that fresh serum was preferable to serum inactivated by heating for use in the complement-fixation test, which they regard as being specially helpful in the diagnosis of early cases of typhus fever in which the Weil-Felix titre has not yet reached a significant level.

[The authors do not seem to have attached importance to the occurrence of low, but rising, titres against *Proteus OX19* as a diagnostic feature in the early stages of typhus fever.]

In discussing the paper, P. Giroud expressed his preference for the rickettsia-agglutination reaction, which he had found simpler and quicker than the complement-fixation test. The latter test also had the drawback of being positive in patients who had suffered from previous attacks of the disease.

John W. D. Megaw

JADIN, J. & GIROUD, P. Typhus exanthématique de l'Urundi, agglutination des rickettsies. [**Exanthematic Typhus in Urundi [Belgian Congo] ; Rickettsial Agglutination.**] *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 11/12, 414–16.

An epidemic of typhus fever occurred in Urundi in 1945–1946, and 23 sera of patients from various localities were tested by the rickettsia-agglutination reaction. Eighteen of these sera agglutinated epidemic-typhus rickettsiae at much higher titres than murine-typhus rickettsiae, and only one gave a reaction suggestive of murine infection, the response being a titre of 1–6,400 with murine rickettsiae against one of 1–3,200 with epidemic rickettsiae.

John W. D. Megaw

RUIZ CASTANEDA, M. **Preparation and Properties of Purified Rickettsial Suspensions.** *J. Immunology.* 1948, Mar., v. 58, No. 3, 283–92, 5 figs. [18 refs.]

Workers interested in the preparations of rickettsial antigen will wish to read this paper in the original text, in which the author gives details of his recent improvements in the methods of purifying and concentrating suspensions of epidemic- and murine-typhus rickettsiae obtained from the lungs of mice and rats infected by the intranasal route.

The suspensions are used for agglutination, complement-fixation, opsonic, and allergic skin tests as well as for the preparation of vaccines.

The author remains convinced that his bivalent lung vaccine is preferable to the commonly used monovalent vaccines because murine rickettsiae can easily be obtained in large quantities from rat lungs, whereas epidemic rickettsiae have to be prepared from mouse lungs, and also because " in Mexico, and perhaps in other countries, murine typhus is not only ' endemic', but also ' epidemic ' when transmitted from man to man by lice".

The bivalent vaccine when given in three doses fell into disfavour in Mexico, but the author believes that a course of five doses given at weekly intervals will afford complete protection.

Photomicrographs are reproduced to show the morphological appearance of the rickettsiae as seen in stained smears and it is stated that the murine rickettsiae occur as small rods of uniform size, whereas the epidemic are pleomorphic and of variable size, but most of them are larger than the murine.

John W. D. Megaw

WALKER, R. H. **Fatal Anaphylaxis following Typhus Vaccine Injection.** *U.S. Nav. Med. Bull.* 1948, Mar.–April, v. 48, No. 2, 303–5. [10 refs.]

FOX, J. P. & PETERSON, O. L. **The Antirickettsial Effect of Thionine Dyes. II. On the Mode of Action of the Thionine Dyes in combatting Experimental Infections of Mice with *Rickettsia orientalis* and *Rickettsia mooseri*.** *J. Immunology.* 1948, Mar., v. 58, No. 3, 299–321. [38 refs.]

In this paper the authors describe the results of studies in continuation of those already reviewed in this *Bulletin* [1947, v. 44, 813].

Toluidine blue and methylene blue in suitable doses were found effective in combatting rickettsial infection in Swiss mice. The strains tested were a Karp strain of *Rickettsia orientalis* and two strains of *R. mooseri*.

A distinct, but less pronounced, effect was caused by six other related drugs : azure C ; azure A ; brilliant cresyl blue ; azure B ; thionin blue ; and selenium methylene blue. A number of other related compounds were found to be ineffective.

The mechanism of the anti-rickettsial effect of the drugs has not been explained, but it is thought to be associated with the chemical structure and known properties of the compounds.

Full details are given of a large number of experiments; these, and the discussion of the mechanism of the action of the drugs, will be of special interest to workers on chemotherapy. Unfortunately the authors cannot hold out any hopes that any of the drugs tested will be useful in the treatment of human rickettsial diseases. *John W. D. Megaw*

SAYERS, M. H. P. & HILL, I. G. W. **The Occurrence and Identification of the Typhus Group of Fevers in South East Asia Command. (Written in 1945.)** *J. Roy. Army Med. Corps.* 1948, Jan., v. 90, No. 1, 6–22, 1 chart & 1 map. [18 refs.]

This paper, written in 1945, contains a useful summary of the occurrence, geographical distribution, epidemiology, special features, and laboratory findings relating to the cases of fevers of the typhus group observed in the hospitals of the South-East Asia Command during the years 1941 to 1944.

Almost all the information contained in the paper has already been published in articles which have been reviewed in this *Bulletin*.

About 5,500 cases were diagnosed during the period and it can safely be assumed that more than 90 per cent. of these were mite-borne. The only outbreak that can with reasonable certainty be regarded as tick-borne was a small group of 33 cases at Ranchi, Bihar, India, in 1943. In the other outbreaks there were a few scattered cases in which a predominating agglutination response of the *Proteus OX2* type or of the combined *OX2* and *OX19* types suggested that the infection may have been tick-borne. There were also a few cases in which a response of the *OX19* type was regarded by the authors as evidence of flea-borne infection. [This type of response is regarded by American observers as occurring frequently in the tick-borne Rocky Mountain spotted fever.] *John W. D. Megaw*

HORTON, R. G., KAREL, L. & CHADWICK, L. E. **Toxicity of γ-Benzene Hexachloride in Clothing.** *Science.* 1948, Mar. 5, 246–7.

Tests conducted by the U.S. Department of Agriculture at Orlando, Florida, have shown that herringbone twill impregnated with 2·0 grams of γ isomer of hexachlorocyclohexane (G.B.H.) per square foot of cloth is highly effective against mites and withstands repeated laundering better than other mite impregnates. But unusual symptoms appeared in 2 workers engaged in preparing batches of the compound for field tests, which suggested that G.B.H. may be absorbed through the skin. In order to investigate this possibility, 40 per cent. acetone solutions of the pure γ isomer, or of a mixture of hexachlorocyclohexanes containing 83 per cent. γ isomer, were applied to the backs and sides of a variety of animals clipped or depilated 24 hours previously, care being ta en to prevent ingestion or inhalation of the compound during the initial 72-hour period of observation. Herringbone twill cloths impregnated by spraying with, or by machine-dipping in, an acetone solution of G.B.H. (83 per cent. γ isomer) of such strength as to yield a concentration of 2 grams of γ isomer per square foot of cloth, were also applied as snugly fitting coats, the covered area of clipped skin per unit body weight corresponding approximately to that for a man in a suit. A number of rabbits and rats died within a few days, displaying symptoms typical of parenterally administered G.B.H. Guineapigs were much less sensitive than the other species. The total loss of G.B.H. from the impregnated suits amounted to 17 per cent. after one wearing,

23 per cent. after two wearings and 36 per cent. after three launderings and no wearings. Bodily motion seemed to contribute to an increased rate of absorption, presumably because small crystals flaked from the fibres and worked into the skin. The authors think it probable that γ benzene hexachloride can be used safely as an impregnate only at concentrations so low as to eliminate any advantages as an insecticide it might possess over other compounds under test.

G. R. Cameron

HUEBNER, R. J., HOTTLE, G. A. & ROBINSON, Eleanor B. **Action of Streptomycin in Experimental Infection with Q Fever.** *Pub. Health Rep.* Wash. 1948, Mar. 19, v. 63, No. 12, 357–62.

Streptomycin has already been shown to have a strongly inhibiting effect on the organisms of epidemic typhus, endemic typhus, Rocky Mountain spotted fever, and rickettsialpox [see this *Bulletin*, 1948, v. 45, 321]. The authors have now found that the drug has a similar action on *Rickettsia burneti*.

With doses proportional to those commonly employed in human therapy, the drug was found highly effective in the treatment of guineapigs infected with large doses of virulent *R. burneti*. The treatment, however, was started much earlier than would be possible when dealing with the disease in man.

A similar inhibiting effect was observed when the drug was injected into yolk sacs just before these were inoculated with *R. burneti*.

In both sets of experiments the action of the drug was rickettsiastatic, not rickettsiacidal.

John W. D. Megaw

YELLOW FEVER

NEGHME RODRÍGUEZ, A. Control del *Aëdes aegypti* en Chile. [**Control of *Aëdes aegypti* in Chile.**] *Bol. Oficina Sanitaria Panamericana.* 1947, Oct., v. 26, No. 10, 852–5. English summary.

Although *Aëdes aegypti* exists along the coast of Chile from Arica to Coquimbo, there have been no outbreaks of yellow fever in that country for 35 years. Arica is an important land, sea and air port and "international crossroads" in the extreme north of the country, and although the port itself is free from *Aëdes*, the Department of Arica, with vast frontiers, adjoins endemic areas in neighbouring countries. The Chilean Government adheres strictly to existing conventions and has signed one recently with the Governments of Peru and Bolivia regarding a campaign against the yellow fever vector.

The foci of *Aëdes* in Arica are some 5 kilometres from the airport: also, seagoing vessels anchor 1 kilometre from the port for health inspection. Despite this, additional measures were introduced in a campaign started in Arica in 1946. These included revision of the census of wells; anti-larval measures; the use of DDT in dwellings and on water deposits; inspection of traffic aerosol bomb fumigation of aircraft; health education; and a biological campaign, consisting of placing *Gambusia affinis* in every water pool or reservoir.

An *Aëdes* index of 40 per cent. in 1945 was reduced to zero in January 1946, and is still maintained there. An outbreak of yellow fever in the Santa Cruz Department of Bolivia caused these measures to be intensified. In 1946, 186 aircraft were inspected and insecticides applied. Vaccination against yellow fever is not provided in Chile: there is no viscerotomy service, as no confirmed foci of jungle yellow fever have appeared in the country up to now.

H. J. O'D. Burke-Gaffney

DENGUE AND ALLIED FEVERS

Ross, S. G. **Dengue Fever at Fanning Island (Central Pacific).** *Med. J. Australia.* 1948, Jan. 17, v. 1, No. 3, 63–6, 2 figs.

Among 46 cases of dengue seen at Fanning Island in 1946 and 1947 there were 32 that were "afebrile" or "nearly afebrile." Nearly all of these modified attacks occurred in persons who had already suffered from the disease during their stay on the island or before their arrival. Similar attacks occurred in two volunteers who allowed themselves to be bitten by experimentally infected *Aëdes aegypti* mosquitoes. One of the volunteers had a typical attack of dengue five years previously; the other had a severe attack six months earlier.

The modified attacks rarely lasted more than four days, the temperature was usually normal; a rash was seen in five of the patients on the face, wrists or ankles; frequent and painful micturition was a prominent symptom; the pains and blood changes were of the types commonly observed in typical cases of dengue.

From a study of the cases the author concludes that there is support for "the theory of tolerance to the virus of dengue after reinfections", but he thinks it probable that "a few different immunological strains of dengue virus are present at Fanning Island" because he saw a few cases of the modified type among persons who had had no previous attacks. *John W. D. Megaw*

Mariotti, M. Febbre da pappataci e febbre delle macerie con eritema persistente facciale quale utile segno di diagnosi postuma. [**Sandfly Fever with Persistent Facial Erythema as a Useful Diagnostic Sign.**] *Acta Med. Italica.* 1948, Jan., v. 3, Supp. No. 1, 26–35. English summary (7 lines).

PLAGUE

Girard, G. Sur un point de terminologie: l'expression *peste selvatique* ou *sylvatique* est fondamentalement erronée. [**"Sylvatic Plague" an Error.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 1/2, 15–16.

A fundamental error in terminology which has gained 20 years start may simply have to be accepted. Girard, however, calls attention to the derivation of the word "sylvatic" from the Spanish *selva* and the Latin *silva*, a wood, and contends rightly that the rodent vectors of this form of plague inhabit steppes and not forests. Sylvatic plague rodents are the tarbagan, the spermophil, the squirrel, the gerbil, the multimammate mouse, and the cui; they dwell in the steppes of Asia or Russia, the plains of America, the deserts of Africa, and the veld of South Africa. Similar objections were taken to the word "Sylvatic" by Adolfo Pozzo [this *Bulletin*, 1946, v. 43, 880] who suggested the description "rural" plague as the antithesis to "port" or "urban" plague. That may apply to South America, but would not apply universally. In fact, Girard maintains that all plague, at least in North Africa, in French West Africa, in Madagascar, in the Netherlands Indies or in British India, whether it be plague of town, village, or jungle hamlet, is murine, and that the only reservoir is the domestic rat. It suffices then to distinguish plague rodents simply as wild and domestic. *W. F. Harvey*

HERIVAUX, A. & TOUMANOFF, C. Epidémiologie de la peste à Saigon-Cholon (1943). L'étude de la faune pulicidienne des rats dans ses rapports avec la transmission de la peste. [**Rat Fleas and Plague in Saigon.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 1/2, 47–59. [12 refs.]

An epidemic of 42 cases of plague in 1943 with 5 sporadic cases in 1944 was the subject of study by the authors. Their tabulated results are presented for rats, mice and muskrats respectively. A hint of caution is thrown out as to deductions from these figures, for the *X. cheopis* index of the epidemic was only 2·63 and never reached the annual mean figure of 5 per rat, which is said to represent an epidemic danger point. The authors found that: on all the animals *X. cheopis* was the predominant flea; there was no correlation between the index and the course of the epidemic; *X. cheopis* was the predominant flea on the mice and *Leptopsylla musculi* was never seen on this animal; *Ctenocephalus* fleas of dogs and cats seemed to have a seasonal prevalence opposite to that of *X. cheopis*; *X. astia* played a feeble, if any, part as a plague vector.

W. F. Harvey

SHARIF, M. **Nutritional Requirements of Flea Larvae, and their bearing on the Specific Distribution and Host Preferences of the Three Indian Species of *Xenopsylla* (Siphonaptera).** *Parasitology.* 1948, Feb., v. 38, No. 4, 253–63. [41 refs.]

Much experimentation by the author has shown that a mixture of dried blood and yeast provides an ideal food for flea larvae, and this has been used as control diet for comparison with other possible diets. The results obtained have been checked statistically for significance and relate in particular to the 3 species of *Xenopsylla* found in India: *cheopis*, *brasiliensis* and *astia*. The irregular distribution, especially of *cheopis* and *astia*, has been the subject of much discussion, as also has the question of the possibility of survival of fleas and their larvae in grain in course of shipment to distant places. In this research attention was concentrated on the suitability of various foods for the flea larvae, as judged by the duration of larval life up to the beginning of pupation or cocoon formation. Ordinarily flea larvae " feed on decaying organic matter containing microorganisms " and it has been determined that " their principal requirements are proteins and vitamins ". The test and control diets used were: (*a*) blood alone, (*b*) highly milled wheat flour devoid of bran, (*c*) blood and wheat flour and (*d*) blood and yeast. One general fact emerged from these experiments, that the deep brown colour and sclerotization of adult fleas obtained from larvae of all three species depended on the presence of haemoglobin in the diets, which again, it is suggested, is dependent on the iron content of the haemoglobin.

The results of the tests were that pure blood was inadequate as a diet for flea larvae, probably owing to deficiency in vitamins. Growth of larvae on pure wheat flour was erratic and probably necessitated the presence of microorganisms. This point, the presence of microorganisms, whether fungi or yeast, is evidently one of great importance and was exemplified by the fact that a mixture of blood and wheat flour, although quickening larval development was not a satisfactory diet. The conclusion is drawn that " larval diets, containing blood or wheat proteins and vitamins of the B group, are essential for the successful rearing of these rat fleas ". From the tests also certain conclusions could be reasonably drawn as to the distribution and host preferences of adult fleas thus: *X. astia* will flourish in the burrows of *Tatera indica* and *Bandicota malabarica*, because these provide the larvae with rich food. On the other hand, *X. cheopis* and *X. brasiliensis* larvae will subsist and develop on much simpler diet and " prosper readily in a burrow of the domestic rat,

even where the nutritive value of the larval food is very low". Temperature tolerance is a factor which is lowest for *X. brasiliensis* and this leaves *X. cheopis* as the flea with a probably wider distribution because of the simpler larval requirements than either of the other two. As *X. brasiliensis* and *X. cheopis* larvae grow better than *X. astia* on flour alone, "this possibly enables them to survive transport in grain even without rats, to places far from their original home". *W. F. Harvey*

QUAN, S. F., FOSTER, L. E., LARSON, A. & MEYER, K. F. **Streptomycin in Experimental Plague.** *Proc. Soc. Exper. Biol. & Med.* 1947, Dec., v. 66, No. 3, 528–32, 4 figs.

Streptomycin, if available, may replace sulphadiazine in the treatment of plague, or possibly, be used along with a sulphonamide and with serum. Details are given of: (1) *Results obtained in vitro.* These showed that streptomycin was bactericidal and appeared to be more active on virulent strains. (2) *Effect on mice and guineapigs infected subcutaneously.* The treatment was by subcutaneous injection, was post-infectional (48 hours), and was more effective than sulphonamide treatment. (3) *Effect on septicaemic plague in mice.* Cure was obtained in 80 to 90 per cent. of non-bubonic septicaemic plague infections, of a type resembling the clinical form of human septicaemic plague, if the treatment was begun early and the doses large. (4) *Effect on pneumonic plague in mice.* "As might be expected 200 to 400 μg of streptomycin hydrochloride . . . every 6 hours, effectively cure 90 to 95 per cent. of the infections." Smaller doses and delay in treatment reduce the chance of cure. (5) *Suggested schedule of treatment in human plague.* Streptomycin, the most effective therapeutic agent yet discovered "for the treatment of bubonic, septicaemic and pneumonic experimental plague infections in mice and guineapigs", should be given in human plague at the earliest diagnosis, in daily doses subcutaneously of 2 gm. in bubonic plague, 4 to 6 gm. in septicaemic and pneumonic plague. The intervals of injection should be 4–6 hours for the first two days, after which the dose may be reduced. It is recommended, however, that to prevent recurrence one gramme should be continued daily for at least 8 days, unless it is more convenient to substitute sulphonamide therapy at this stage. The simultaneous administration of potent antiplague serum may be required in profound toxaemia. *W. F. Harvey*

POLLOCK, J. S. M. **Plague controlled in Haifa by the Use of DDT alone.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 647–56, 2 figs.

The efficient control of human plague would seem to be in sight, and the author hopes that "the world has seen its last widespread plague epidemic". Immediate measures are designed to break the rat-flea-man chain by attacking the flea with DDT. Treatment of patients proceeds as usual, reliance being placed on sulphadiazine and streptomycin. Long term measures may be taken up, as and when possible. Experience in previous outbreaks was of thousands of pounds spent on anti-plague measures and yet without influence on the course of the epidemic.

Haifa is probably a fairly typical Turkish town of olden times. A main paved sewer runs from end to end of the old city and from May till November never runs full. Its sides are shelved and give both ideal runways and breeding places for the sewer rat. Dwellings are crowded; each has a dark damp basement, which is, under present circumstances, itself a human habitation and has direct branch communication with the main sewer. The

port of Haifa on the other hand is quite modern, but is closely linked with the old city; it is a busy inward and outward port and is provided with extensive grain and food stores.

The first case of bubonic plague in the outbreak under review was admitted on 26th June 1947 and proved fatal. Full-scale plague precautions were immediately taken in five sectors of the city, in each of which a DDT team laid down 5 per cent. residual spray, using the Four Oaks Knapsack sprayer. Impedimenta were cleared by labourers. A sixth team was mobile for the spraying of "house and work place of each suspected case" and their surroundings. It was possible with this organization to lay down 500 gallons of DDT spray daily. At the same time, great publicity was given to the need for residual spray in houses, and 10 per cent. dusting powder for bodily use. Centres were set up at which power-driven compressor blowers were used for dusting purposes and these centres became very popular with the specially important, lower class, Arab population. As many as 30,000 persons were dusted in the first 10 days.

The last plague case seems to have occurred on 19th July. "In all nineteen bacteriologically proved cases of plague were treated in the Government Hospital, Haifa"; all of them were bubonic. Six other cases were clinically bubonic, but not proven bacteriologically. Only one case, the first, proved fatal. "The circumstantial evidence produced in this outbreak would indicate that by using DDT as the first line of attack, together with a modified 'cordon sanitaire', rat extermination, while important, may take secondary place and should be planned on a long-term continuous preventative basis".

W. F. Harvey

NICHOLSON, H. P. & GAINES, T. B. **A Comparison of the Effectiveness of 5 and 10 per cent. DDT Dusts for the Control of Rat Fleas.** *Pub. Health Rep.* Wash. 1948, Jan. 30, v. 63, No. 5, 129–36, 4 figs.

Field studies were made in July 1946 at Columbia, S.C., U.S.A., to determine the value of dust containing 5 per cent. DDT and 95 per cent. pyrophyllite for the control of rat fleas, and to compare the results with those obtained in 1945 in Savannah, Ga., where 10 per cent. DDT dust was used.

The rat-infested establishments were shops, cafés, warehouses, etc., in both places, and similar premises were used as checks. The insecticide was applied to the rat burrows by dust gun and to the runs by shaker; photographs of this equipment are given. All rats trapped (except six *Rattus rattus* in the Savannah test) were *Rattus norvegicus*. The fleas were predominantly *Xenopsylla cheopis*, the following species being rare both in treated and untreated establishments: *Nosopsyllus fasciatus*, *Leptopsylla segnis*, *Echinophaga gallinacea* and *Ctenocephalides felis*.

The rats were trapped before treatment, 6 to 8 days after treatment, then at intervals of 6 weeks for about three months. Because of the scarcity of other species, comparison of results is based on the effects on *X. cheopis*.

The rat flea populations were almost completely eliminated within a week after application of both the 5 per cent. and the 10 per cent. DDT dusts in every type of treated premises. There was no significant degree of recovery after three months, and no significant difference in the results of the two formulations; the maximum duration of effective control could not be determined.

H. S. Leeson

CHOLERA

UNDERWOOD, E. A. **The History of Cholera in Great Britain.** *Proc. Roy. Soc. Med.* 1948, Mar., v. 41, No. 3, 165–73 (Sect. Epidem. & State Med. 1–9), 1 fig. [37 refs.]

The history of cholera in Great Britain is one of little more than 100 years. True cholera was known as Asiatic and on its arrival had to be distinguished from the simple indigenous " cholera nostras ". The first death from true cholera in Britain occurred in Sunderland on October 20, 1831. Cholera then spread epidemically, affecting the north of England and south and mid-Scotland; later it spread to England generally. At first cholera was regarded as a visitation of Divine Providence and as a catastrophe in the lives of the poor. This opinion seems to have changed somewhat when cholera became a pestilence sparing " neither age nor sex nor station ". Much discussion raged on whether cholera could be called contagious, and Snow's essay of 1849 was entitled " On the Mode of Communication of Cholera " ; it was followed by his further publications. He asserted his belief that the excretions of the sick contained the contaminating material and by multiplication in the small intestine gave rise to the disease. He also promulgated the doctrine of water-borne cholera, which received strong support from the episode of the Broad Street Pump in St. James's Parish in London. The Board of Guardians ordered removal of the pump handle and the incidence of new cases in this area ceased almost at once.

The epidemics of cholera in Great Britain caused " the deaths in England and Wales alone of 21,800 persons in 1832 ; 53,292 in 1848–49 ; 20,099 in 1853–54 and 14,378 in 1866 ". The 1832 epidemic and subsequent visitations have close connexions with the establishment of social reforms, formation of the great Prudential Insurance Company, and the building up of " quarantine and other measures which have kept this island almost inviolate for eighty years ".

W. F. Harvey

TAYLOR, J. **Epidemiology of Cholera.** [Summary]. *Proc. Roy. Soc. Med.* 1948, Mar., v. 41, No. 3, 174–6 (Sect. Epidem. & State Med. 10–12).

Most of the points made in this important communication have already been summarized [see this *Bulletin*, 1948, v. 45, 175]. It may be well to add that the actual mode of introduction into Egypt of the first infection has not been established. " So far we have no definite information on how infection was introduced to Egypt at a time when the disease had not been reported as occurring in any other country west of India. Air or sea carriage from the East must be presumed ".

W. F. Harvey

WHITE, P. B. **Bacteriological and Immunological Aspects of Cholera.** [Summary.] *Proc. Roy. Soc. Med.* 1948, Mar., v. 41, No. 3, 176–7 (Sect. Epidem. & State Med. 12–13).

A remarkable interest attaches to this communication because of its author and his connexion with the application of " the receptor analysis methods of Weil and Felix " to the conception of a true cholera vibrio. Very great advances were made, but there is still disputation on the subject. One of the current dicta is now abandoned. Bruce White finds indisputable evidence of the transmutability of Ogawa and El Tor vibrios to Inaba vibrios by " focusing the serous influence " on the type-specific O antigen, with the use of strictly monospecific antisera. Thus he establishes the fact that " the types are not separate species or subspecies, but phases of a single species " and describes this finding

also as " something like the specific and non-specific phases of the Salmonella". At the same time he expresses agreement with the view reached by Sir John Taylor on the collected results from an attempt to classify 311 vibrio strains, inagglutinable with O group 1 serum, that " with one possible exception, no case for the cholerigenic activity of any of these could be made out ".

W. F. Harvey

GOHAR, M. A. **Isolation of the Cholera Vibrio.** *J. Trop. Med. & Hyg.* 1948, Mar., v. 51, No. 3, 59–60, 1 fig.

Two labour-saving methods for speedy isolation of the cholera vibrio in times of epidemic are here described. The first requires a 25 ml. conical flask filled with alkaline peptone water to the bottom of its neck, thus giving a concentration within a small surface area of the strongly aerobic vibrio growing rapidly from the faeces inoculum. Growth is taken from this surface to a semi-sloped mannite Andrade agar to which has been added about 1 ml. peptone water, thus providing a composite stab, slope and peptone water culture. The second improved method, especially useful for examination of convalescents or carriers, omits the preliminary enrichment and selection. The faecal matter, or vomit, is inoculated into a wide tube, 3 cm. in diameter, containing 0·5 per cent. agar dissolved in alkaline peptone water, in which a piece of glass tubing about 6 cm. in length and 3 mm. in diameter is immersed. The medium rises in the small tube, and is to be covered by about 5 mm. height of alkaline peptone water. After inoculation of the large tube, its surface is covered with a thin layer of sterile liquid paraffin, to seal it. In this method advantage is obviously taken " of the active motility and strongly aerobic character of the cholera vibrios ", which " leads to their concentration in the only part exposed to the air ", in the small immersed glass tube. The further examination is according to routine.

W. F. Harvey

GALLUT, J. Sur le mécanisme de la réaction du choléra-roth. [**Mechanism of the Cholera-red Reaction.**] *Ann. Inst. Pasteur.* 1948, Jan., v. 74, No. 1, 27–39, 5 figs. [11 refs.]

Those who would follow the argument presented should read Gallut on the utilization of glucose by the cholera vibrio [this *Bulletin*, 1947, v. 44, 660 and 1948, v. 45, 177] as well as the work of SEN and his fellow workers [*ibid.*, 1947, v. 44, 209]. The essence of the cholera-red reaction is the ability of the cholera vibrio to transform nitrates and to produce indole from peptone. As the production of nitrites is practically independent of the method of culture, the variation in positiveness of the colour reaction must be based on the conditions for development of indole, except that the colour quality is conditioned by the nitrite indole ratio : orange for a value greater than 1, red (" solferino ") for a value between 1 and 2, and violet if greater than 2, when the concentration of indole is more than 50 mgm. per litre. Apart from these facts and the fact that in a glucose medium the production of indole, and therefore the cholera red reaction, is independent of the oxidation-reduction potential, we have to consider especially the part played by glucose in the reaction. In the total absence of glucose it is a simple reaction ; if glucose is present, the reaction demands its complete combustion, as distinct from fermentation producing acidity fatal to the vibrio, before it can be manifest. Moreover there are certain limits of concentration of the glucose within which the reaction can take place and which provide the time-table conditions for its optimum appearance. Other factors which come into play are those of anaerobiosis, aerobiosis and aeration of the medium.

W. F. Harvey

Pasricha, C. L., Paul, B. M., Das Gupta, A. C. & Das, A. K. **Sulphasuxidine in the Treatment of Cholera.** *Indian Med. Gaz.* 1947, Nov., v. 82, No. 11, 657.

" Sulphasuxidine in the dosage used had no effect in reducing the mortality in cholera. No untoward effects were noted in cholera cases after its use."

Pasricha, C. L., Paul, B. M., Das Gupta, A. C. & Das, A. K. **Phthalylsulphathiazole in the Treatment of Cholera.** *Indian Med. Gaz.* 1947, Nov., v. 82, No. 11, 656–7.

" Although the death rate (7·3 per cent.) is less in the phthalylsulphathiazole series than in the control series (10·1 per cent.) the difference is not significant."

i. Bhatnagar, S. S., de Sa, J., Fernandes, F. & Divekar, P. V. **Chemotherapy of Cholera with a New Sulphonamide Compound (" 6257 "). Laboratory Investigations and Field Trials.** *Brit. Med. J.* 1948, Apr. 17, 719–23. [15 refs.]

ii. British Med, J. 1948, Apr. 17, 738–9. **The Chemotherapy of Cholera.**

i. Sulphaguanidine has been used in the treatment of cholera, but has not been conspicuously successful even where it was combined with hypertonic saline. Now the prospect appears of direct therapy with a new sulphonamide compound, which differs from the older compounds in not being a substitution derivative of sulphanilamide but a condensation formed by the molecular combination of two compounds, sulphathiazole and formaldehyde. Laboratory investigation showed that this preparation was markedly bactericidal and inhibitory. Animal experiments were carried out on mice and these involved both pre-infectional and post-infectional therapy, of 40 mgm. daily for 4 days in the latter case, with groups of 20 animals each for intraperitoneal and subcutaneous routes. The test intraperitoneal dose of virulent Inaba vibrios did not exceed 2 MLD., so as not to kill animals by toxic effect and the protection reached 100 per cent. Oral therapy in the experimental animals was not so effective and saved only 20 per cent., while the control group mortality was 100 per cent. The drug, owing to its low solubility in water, was given as a 20 per cent. suspension in 2 per cent. gum arabic. Absorption and excretion are both slow so that it is easy to maintain a long and effective blood concentration.

In the field, so far as first trials have gone, results are very satisfactory with the extraordinary saving of 82 patients out of 85 treated. Moreover " the patients were treated in their homes without the benefit of nursing and general medical care and no complementary treatment . . . was resorted to ". One advantage of treatment at home was, of course, the saving of an exhausting journey to hospital. The authors rightly stress that control of an epidemic of cholera by 7 days of therapy, producing complete freedom of the stools from infective vibrios, is an event of major importance. That applies also to the use of the drug prophylactically in carriers who, if treated before panic or pilgrimage dispersal occurs, may be rendered harmless. The average amount given over 7 days was 16 gm. for a child, 23 gm. for a woman and 25–30 gm. for a man.

In one important respect the field trials differed from the animal experimentation in that administration was more successful by the oral route than by subcutaneous inoculation. No appreciable toxic effects were observed, even with a 50 gm. dose : if cholera vomiting was extreme the drug was given in 0·5 gm.

tablets instead of powder. Coma and hyperemesis required high colonic administration. " Six to eight hours after starting treatment purgation diminished and vomiting stopped. By the ninth hour as a rule the patient had passed water."

ii. The final editorial comment on this account is : " The results achieved in Madras . . . are so striking that they merit further investigation on the widest possible scale ". The drug may well have wider use than in the treatment of cholera. *W. F. Harvey*

KOPANARIS, P. **Cholera in Egypt and Preventive Measures taken in Greece.** *Arch. d'Hygiène.* Athens. 1947, Apr.–Dec., Nos. 4/12, 89–104.

That cholera might spread from Egypt to Greece and, like a military invasion, through the Balkan countries to Central Europe was a very natural supposition. According to Kopanaris, Egypt in the last century was the reservoir country from which cholera spread to Europe and America. Those days have almost been forgotten and the present epidemic in Egypt has been an unpleasant reminder of what might occur again ; nor can it be said that, although the danger has subsided, it may not recur in the near future. Energetic measures were taken by the public health authorities in Greece and every help was afforded in the way of information by the Egyptian authorities. All seaports were closed to arrivals from Egypt with the exception of the port of Piraeus. An equal, if not greater danger, was that of arrival of a case, or incubating case, by air, and Hassani was detailed to be the only receiving airport. Account was taken of the incubation period of 5 days and all persons not possessed of a valid inoculation certificate were subject to detention for this time, if they were entering Greece itself. The quarantine island of Aghios Georgios in the port of Piraeus served for both air and sea passengers. If they had not been inoculated they received prophylactic vaccine here. Stools were examined and of the 662 detained persons none gave a positive result. Persons in transit only were not detained, but were not allowed to leave the airport itself nor were the crews allowed to mingle with the general population. Mail, food and merchandise all received particular control ; mail required disinfection ; transportation of fresh food, fruit and vegetables from Egypt was forbidden. Apart from all the regular procedures, the emphasis here is laid upon the use of prophylactic vaccine. Three reports are given dealing with manufacture, antigenic strain of vibrio, potency and so on. The vaccine prepared in the State Laboratory contained about 8,000 million vibrios per cc., was tested for potency against standard commercial vaccines with satisfactory results and was used for inoculating over 800,000 people " without unpleasant effect ". The vaccine was prepared from the following 5 strains : Inaba, form AC (N.I.H. 41, United States) ; Ogawa, form AB (N.I.H. 35A3) ; Hikojima, form A (No. 5122, N.I.H., China) ; Hikojima, form B (No. 5053, N.I.H., China) ; El Kurein, 495, isolated during the recent Egyptian epidemic. Plans were " made and put into effect for progressive inoculation of the population in Piraeus and Athens " and special attention was paid to " persons who, due to their professions lived under unfavourable conditions. Such persons were street-cleaners, rag-pickers, sewage disposers etc." Again priority in inoculation " was given to the vocations which presented the greatest danger of infection ". The Government do not propose to "reduce the prophylactic and sanitary measures taken in Greece", even with the abatement and disappearance of the epidemic meanwhile in Egypt. *W. F. Harvey*

RELAPSING FEVER AND OTHER SPIROCHAETOSES

BOIRON, H., KOERBER, R. & CARRONNIER, B., Mlle. A propos d'un cas de récurrente hispano-africaine importé à Dakar. Transmission de *Spirochaeta hispanica* par l'ornithodore et par le pou. [**Concerning a Case of Spanish-African Relapsing Fever imported at Dakar. Transmission of** *Spirochaeta hispanica* **by** *Ornithodorus* **and by the Louse.**] *Bull. Soc. Path. Exot.* 1948, v. 41, Nos. 1/2, 81–9. [16 refs.]

During 1945, various cases of relapsing fever were diagnosed in Dakar among Africans repatriated from North Africa, and while most of these cases were of typical *S. recurrentis* infection, one of them was found to be of the Spanish-African type.

The patient had come from Morocco where he had been infected with relapsing fever two months previously, and the attack at Dakar is considered to have been a relapse. Cerebrospinal fluid and blood from the patient were inoculated into two guineapigs, both of which became infected. Subsequently the strain was inoculated into monkeys which were found to be very susceptible, and showed 2 or 3 relapses. Guineapigs were also very susceptible, but mice only moderately so, confirming the diagnosis of *S. hispanica*.

The authors fed both *Ornithodorus erraticus* and body lice on a monkey whose blood contained numerous spirochaetes. The ticks became infected and subsequently transmitted the infection by bite. The lice were fed on this infected monkey for 5 successive days, then for 7 days on a normal monkey, which showed no sign of infection. A monkey inoculated with the contents of these lice 4 days after the last infective feed developed a typical infection.

In a second series of experiments, 176 normal lice were fed on a monkey whose blood showed 8 spirochaetes per field, and subsequently were maintained on a normal human subject for the 23 following days. Each day a certain number of lice were ground up and after dark-ground examination were inoculated into normal mice, except on two occasions when monkeys were used. From the 4th day onwards, with only 4 exceptions, all the inoculated animals became infected. The lice were negative to microscopical examination for the first 10 days and then became positive, the numbers of spirochaetes reaching a maximum after 19–20 days and then again disappearing for 2 days to reappear in small numbers the last 2 days.

These results show that at least the strain of *S. hispanica* examined by the authors may be transmitted by means of both *Ornithodorus erraticus* and the louse. *E. Hindle*

HEISCH, R. B. & GARNHAM, P. C. C. **The Transmission of** *Spirochaeta duttoni* **Novy and Knapp by** *Pediculus humanus corporis* **de Geer.** *Parasitology.* 1948, Feb., v. 38, No. 4, 247–52. [11 refs.]

The hypothesis that tick-borne spirochaetes may become adapted to transmission by lice has hitherto received no support from experiments with *Spirochaeta duttoni*, but the present interesting paper records the transmission of the East African strain by *Pediculus corporis*.

Various batches of lice collected from a "clean" area (Nairobi), were first fed two, three or four days on monkeys heavily infected with the local strain of *S. duttoni*, and then twice a day on the authors. After various intervals the lice were examined by dark ground illumination for the presence of spirochaetes and also emulsions of them were inoculated into monkeys or mice.

The cyclical development of the spirochaete in lice was observed in seven experiments and in the last four the same strain was transmitted through four successive batches of lice. The lice were infective the day after their infective meal, but were negative on the 3rd, 4th and 6th days, but positive on the 5th and 7th. No actual spirochaetes were seen in these lice and proof of infection depended on animal experiments.

The authors are of the opinion that the infections produced by lice during the first 10 days after an infective feed are caused by the organism in an invisible phase.

The cycle of *S. duttoni* in the louse seems to differ from that of the East African strain of *S. recurrentis* as the latter shows a more definite negative phase. [See this *Bulletin*, 1948, v. 45, 86.] In both, however, the negative cycle is terminated by the appearance of slender, cork-screw-shaped metacyclic forms about the 15th day.

The course of the louse-transmitted *S. duttoni* infection, in monkeys, mice, and a rat and a hedgehog, is given in tabular form. The results show that in pathogenicity it resembles the tick-transmitted infection. Moreover, the results of cross-immunity tests clearly indicated that the infection in animals after the fourth transmission by means of lice, was serologically identical with the ordinary strain of *S. duttoni* and distinct from *S. recurrentis*.

E. Hindle

NASR, L. A. **Sterile Splenic Abscess after Relapsing Fever.** *Lancet.* 1948, Apr. 10, 555–8, 3 figs.

This paper is based on 7 cases admitted to the Kasr-El-Ainy Hospital, Cairo, between April and June 1946, during the decline of the epidemic of relapsing fever which attacked Upper Egypt during the winter of 1945–1946. Splenic abscess in relapsing fever is a rarity, EL-RAMLY [this *Bulletin*, 1948, v. 45, 185] finding only 23 instances in 3,000 consecutive cases treated during the epidemic of 1945–1946: of 139 fatal cases, splenic infections were found at necropsy in 28, of which 16 showed abscess formation.

In the present series, 4 were males and 3 females, and all gave a history of relapsing fever. The 3 females had had neoarsphenamine (2 or 3 injections, dose not stated).

The condition began with sudden pain, usually described as severe, under the left costal margin, in some cases referred to the left shoulder or epigastrium and usually subsiding without treatment.

In all cases there was an interval, after the pain had subsided, before abdominal swelling was noticed, and it was only after this mass had become very large, that medical advice was sought. One patient sought advice for cough and pain in the chest, at a time when no mass was palpable in the abdomen; this developed in three weeks after the onset of pain. Where no chest complications were present there was no change in general health, pulse, or temperature, but where the chest was involved the patient had fever, dyspnoea, raised pulse, and toxaemia.

The liver was enlarged and tender in most cases. The splenic enlargement differed from the usual type in that (1) it did not move on respiration, but was firmly fixed; (2) its borders were rounded and a notch was felt in one case only; (3) it was cystic, and was tender in the early stages; (4) in one case there was shifting dullness in the spleen; (5) Traube's area was dull even in cases with no left pleural effusion. The size of the spleen varied, the smallest reaching a finger-breadth above the umbilicus, the largest nearly to the right iliac fossa.

Pleural effusion was present in 2 cases when they were first seen, the effusion in both being sterile and requiring repeated aspirations. Some of the early cases were misdiagnosed as retroperitoneal sarcoma, renal tumour, etc. One patient was first seen still complaining of the initial pain without enlargement of the spleen and the case was mistaken for pleurisy with effusion. Radiography always showed a raised immobile left dome of the diaphragm.

No malaria or relapsing fever parasites were found and, apart from one case of secondary infection, there was no rise in the polymorphonuclear leucocytes, even with a high leucocyte count. The Wassermann reaction was positive in the 4 cases where it was tested.

In the earlier cases, penicillin or sulphadiazine or both were given before operation, with no apparent good result. Splenectomy was not attempted in any cases owing to the dense adhesions and fixation of the mass, the abscess being drained through a separate left subcostal incision.

Unless secondary infection is present, penicillin and sulphonamides are not required and in early cases simple drainage results in cure. Post-operative complications were (1) left pneumonia followed by empyema, and (2) secondary infection from the operation sinus.

The spleen was transformed into a large sac with a dense fibrous wall, a rim of spleen tissue being found at the lower pole which was free. The abscess cavity was usually single and lined with shreddy necrotic tissue. The liver was enlarged and in some cases very congested.

The pus was odourless and usually a dull greenish-yellow colour, viscid and slimy. It was sterile in 6 cases, in 1 case *Staph. aureus* was found. Early lesions showed much necrosis and aseptic suppuration compatible with the formation of a sterile abscess but not hitherto described in relation to relapsing fever. [This complication must be a very rare one.] *C. F. Shelton*

Ortuzar, R., Pozo, S. & Rosati, S. Sodoku, septicemia a estreptococo moniliforme y fiebre de Haver Hill. [**Sodoku,** *Streptococcus moniliformis* **Septicaemia and Haverhill Fever.**] *Rev. Med. Chile.* 1947, Dec., v. 75, No. 12, 774–8, 2 figs.

This is another attempt at solving the problem of rat-bite fevers, Haverhill fever and that produced by *Streptobacillus moniliformis*. There is no little obscurity regarding these conditions. Sodoku is known to be due to *Spirillum minus* (*Spirochaeta morsus muris*); Haverhill fever is regarded as a form of rat-bite fever, but the spirillum is not found and *Streptobacillus moniliformis* can be cultivated. On the other hand, cases of Haverhill fever are recorded in which rats or rat-bites cannot be incriminated [see this *Bulletin*, 1942, v. 39, 693]. A full table giving the distinctive characters of sodoku and rat-bite Haverhill fever is reproduced in this *Bulletin*, 1944, v. 41, 943. The present authors see three distinct diseases in this group, namely, sodoku, a septicaemia due to *Streptobacillus moniliformis* inoculated by the bite of a rat, and Haverhill fever due to the same organism, but conveyed by contaminated food and not by rats, and they give in the accompanying table the distinguishing features.

[Since Haverhill fever has been shown, in some cases at least, to be due to rat-bite, it seems incorrect to restrict the name, as the authors have done, to the syndrome unassociated with such a history. Would it not be better, for the present at all events, to discard the name Haverhill fever and divide the three under two main headings: fever due to *Spirillum minus* and diseases due to infection by *Streptobacillus moniliformis*, and subdivide the latter into that associated with the bite of a rat and that associated with contaminated food ?]

	Sodoku	Septicaemia due to *Streptobacillus moniliformis*	Haverhill Fever
1. Causal agent	*Spirillum minus*	*Streptobacillus moniliformis*	*Streptobacillus moniliformis*
2. Mode of infection ...	Bite of rat ...	Bite of rat ...	Contaminated food
3. Incubation	1–3 weeks ...	1–3 days ...	3–6 days
4. Local chancre and regional lymphadenitis	Marked	Slighter	Absent
5. Septicaemia	Moderate ...	Marked	Dominant
6. Cutaneous erythema	Marked; macular and papular	Marked; papular, morbilliform	Morbilliform, petechial, polymorphic
7. Joint involvement ...	Absent	Commonly present	Usual feature
8. Splenomegaly ...	Absent	Commonly present	Usual feature
9. General adenopathy	Absent	Occasional ...	Frequent
10. Cyclic course ...	Absent	Frequent ...	Frequent
11. Haemoculture ...	Negative ...	Positive	Positive
12. Effect of Arsenic ...	Good	Little or none ...	Little or none
13. Effect of Penicillin ...	Slight	Good	Good

Notes of 5 cases are given: one of sodoku, one of *S. moniliformis* septicaemia from a rat-bite and resembling sodoku, one designated "glandular form of Haverhill fever", but with no history of rat-bite, one of epidemic arthritic erythema (Haverhill fever) with general adenitis, and one of *S. moniliformis* septicaemia with a valvular endocarditis associated with this organism and ending fatally.

H. Harold Scott

Noury, M. Contribution à l'étude du sodoku et recherche sur l'action du sérum antispirelle. [**Contribution to the Study of Rat-Bite Fever and Research on the Action of Anti-spirillum Serum.**] *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 11/12, 430–35.

Immune serum was prepared by inoculating sheep over a period of 14 months with blood and emulsions of liver and spleen taken from guineapigs infected with *Spirillum minus*. Spirilla were never found on microscopical examination of the sheep's blood, but the organism could be demonstrated by subinoculation of guineapigs or mice.

The lytic action of the serum *in vitro* was examined in 3 tests.

(1) 1·0 ml. amounts of a 1 : 5 dilution of blood from a guineapig heavily infected with *S. minus* were mixed with undiluted serum in quantities from 9 to 2 ml. The mixtures, and a control containing 9 ml. of normal saline, were incubated for 2 hours at 35°C. Doses of 1 ml. were inoculated into guineapigs, 3 being used for each dilution.

(2) 2 ml. of a similar 1 : 5 blood suspension were mixed with 1·6 to 0·2 ml. serum, incubated 2 hours at 35°C. and made up to 4·0 ml. with normal saline. Again 3 guineapigs were inoculated from each dilution.

The control animals died in every case, but not a single guineapig which received the mixtures containing serum, showing that the antiserum had completely inhibited the spirillum.

(3) The infected material in this case consisted of a mixture of blood and emulsion of liver and spleen. Volumes from 9·9 to 8·0 ml. were mixed with antiserum in amounts to give a final volume of 10 ml. (0·1–2 ml. serum), and incubated as before. In this test, 2 guineapigs were inoculated from each dilution. The controls died, but the results of the serum mixtures were indefinite. Most of the animals became infected after long incubation periods, showing that the serum had only retarded the development of disease.

Serum from normal sheep and from syphilitic patients had no inhibitory action. The effect is therefore specific to anti-spirillum serum.

Prophylaxis was tried by injecting serum [dose not given] into guineapigs 2–4 days before infection. No protection was obtained. Attempted treatment of infected animals with serum was also ineffective. *J. C. Broom*

LEPROSY

CHAUSSINAND, R. Sexe et lèpre. [**Sex and Leprosy.**] *Internat. J. Leprosy.* Cleveland, Ohio. 1947, Oct.–Dec., v. 15, No. 4, 406–16.

This is a careful survey of the question, based on extensive data and it brings out some new points. The author found 75·5 per cent. of 1,002 cases to be in males, in accordance with general experience. Age curves show little difference in the first decade and after the 45th year, and the greatest preponderance of males between the ages of 15–20 ; this is attributed to a much larger number of males who contract the disease outside their families owing to great promiscuity in the course of their work and to greater susceptibility attributable to endocrine differences. In another table, 4–5 years are allowed for the incubation period and the probable dates of contamination in the two sexes are shown for each five-yearly period. The curves of these data show that up to the age of 15 there was a slightly higher percentage of infections among female children, after which the percentages fall in both sexes but more rapidly in females, who are less exposed to extrafamilial infections. The curve of females also shows slight rises between 25–29 and 40–44 ; that is, during the period of most active gestations and at the commencement of the menopause, which somewhat increase the susceptibility of females, and are indications of the influence of endocrines. The benign nerve form is rather more frequent among females, and another table and curves of the age, sex and type on admission show a preponderance of the nerve form in males up to the age of 9, and a very large one in females of 40 and upwards. On the other hand, the lepromatous form is much more prevalent among females up to 29 and in males over 39 years of age. Thus, in general, the evolution is more serious in males, and females show more resistance except at an early age and during the period of gestation. All the data are based on experience in Cochin-China. *L. Rogers*

HARBITZ, F. Lepraforsking i Norge gjennom hundre år. [**Leprology in Norway during a Century.**] *Nordisk Med.* 1948, Apr. 2, v. 38, No. 14, 677–9.

The English summary appended to the paper is as follows :—

" This centenary address gives a survey of Norwegian contributions to leprology : the great descriptive paper by DANIELSSEN & BOECK published in

1847 ; the discovery of the lepra bacillus by ARMAUER HANSEN probably made in 1873 and reported in his paper of 1874 ; finally the extensive studies on the pathology and epidemiology of the disease made by LIE. To the work of these men is largely due the fact that lepra has been practically eradicated in Norway, the number of cases having decreased from 3,000 in 1856 to 23 in 1943 (the latest figure available)."

LENGAUER, L. **Leprosy in the Benin and Warri Areas of Nigeria.** *Leprosy Review.* 1948, Jan., v. 19, No. 1, 14–20.

These provinces are in the low-lying Niger delta, with a hot humid climate ; they are sparsely populated, but the percentage of infective cases is large, with many lepromatous cases in children and much nodular involvement. The majority of cases commence with a single depigmented macule, but in some an ulcer of the foot is the primary lesion. More than one type of lesion may be seen at the same time. Some bacteriologically negative tuberculoid cases may become positive lepromatous ones after one or two years, usually without any acute phase or reaction. Puberty and pregnancy periods may show marked deterioration of the leprotic condition. The tendency of tuberculoids to become lepromatous can be arrested by regular treatment. Early lepromatous cases may show a diffuse, undefined blush when seen in a good light. An unusual feature is ulcerating nodules on the male genitalia ; stenosis of the urinary meatus may result. Blindness is rare ; only three cases were seen among some 500 lepromatous patients. Extensive involvement of the larynx is extremely common. Albuminuria is common. In three cases, death occurred during reactions, although they are not common. As many as 112 tuberculoid cases occurred among 185 non-infectious cases. Prognosis is better in tuberculoid lesions of the face and extremities than with those on the back. The author has not seen self-healing in leprosy. Mutilation of the hands and feet is common in all types. Non-infectious cases are very prone to ulceration, and the majority of deaths are due to septic infections in untreated cases. Rapid progress and quick change of type make classification and prognosis very difficult. This rapid evolution of types calls for research.

L. Rogers

RYRIE, G. A. **The Macular Syndrome in Nigeria.** *Leprosy Review.* 1948, Jan., v. 19, No. 1, 35–9.

In this note the author records a preliminary study he made during a recent tour of S. Nigeria. He uses the term "macule" to denote an unelevated small discoloured patch of skin ; it usually appears as an initial or primary small lesion of 1–5 or more centimetres in diameter. Multiple macules are essentially a secondary phase, the earlier lesion often being overlooked. In Africans, macules are well-defined, depigmented and of a *café-au-lait* colour, usually with some faint erythema. No bacilli are to be found and there is no tactile or thermal anaesthesia. They are differentiated from tuberculoid or neural macules by absence of any loss of sensation. They may either fade and disappear or spread slowly with a tendency to coalescence, or a reaction may occur in the form of a sudden outbreak of a crop of macules, usually on the trunk. They occasionally become bacteriologically positive ; but the prognosis is usually good under treatment. Rarely this form of leprosy may become tuberculoid or lepromatous ; it is very common in Nigeria. [The above series of papers illustrate the protean nature of leprosy.]

L. Rogers

Ross, C. M. **Some Differences in the Leprosy of the Gambia and Nigeria.** *Leprosy Review.* 1948, Jan., v. 19, No. 1, 12–14.

This note is based on a survey of 17,000 Gambia people in three areas extending up the river, with much lower humidity in the inland areas. The social conditions and diet are poor; meat is rarely eaten, and vitamin B is deficient; eye lesions and rickets are common. Clinical and bacteriological examinations were made in all suspected cases. The percentages of different types were: lepromatous 13·5 per cent., tuberculoid 71·0 per cent.; and unclassified 15·5 per cent. As compared with experience in Nigeria, lepromatous nodules were larger and they were present on the mucous membranes. In tuberculoid cases, a greater proportion showed erythematous reacting conditions. In a young female, small tuberculoid macules half encircling her body had the distribution of herpes zoster. The lepra bacilli in slides were relatively more numerous in each of the three types than in Nigeria, and scantily positive slides were astoundingly common in tuberculoid cases as compared with the negative results found in the Owerri Province of South Nigeria, and 19 to 40 per cent. of tuberculoid cases were thus scantily positive. Unclassified cases showed 85 per cent. to be positive. Nerve involvement was also more frequent. The highest incidence was found in the vitamin-deficient upper river area, and the lowest at the mouth of the river where there were better conditions as regards vitamins and social aspects. *L. Rogers*

Ryrie, G. A. **Regional Differences in Leprosy. Leprosy among Chinese in Malaya.** *Leprosy Review.* 1948, Jan., v. 19, No. 1, 4–11, 1 graph.

This is an interesting comparison between the types of leprosy seen among Chinese, Malays and Indians in Malaya, based on a large experience.

The disease is most virulent among Chinese and least so among Indians, three-fourths of the cases among the latter being of mild tuberculoid disease with a tendency to self-healing, but among the Chinese only one-third are of the tuberculoid type. The climate of Malaya is of the hot humid type, in which leprosy flourishes. On the other hand, a higher standard of living than in India tends to hinder the spread of the disease. The age incidence is important. Among the Chinese, early macules are commonly found in children of 5 to 15 years of age, most of which tend to clear up, but in about one-fourth tuberculoid lesions develop and may go on to the lepromatous condition, especially if the onset of the tuberculoid stage occurs early. When a reliable history is obtained in Chinese, in nearly every lepromatous case a tuberculoid stage was first observed, commonly in the age group 16–40. In a smaller number of persons of over 40 years of age, the proportion of tuberculoid cases is very much higher, but the tendency to become lepromatous is very much less. Major tuberculoid cases are more liable than minor to become lepromatous, but nerve thickening in tuberculoid leprosy is less evident in Chinese than in Indians, and it is rare in children and in those over 40. In view of the foregoing peculiarity of the evolution of leprosy in tuberculoid cases in Chinese subjects, active treatment is necessary, in order to prevent them becoming lepromatous. For this purpose, intradermal injections are of little value and they tend to obscure any evolutionary changes. Hydnocarpus oil or esters (deep subcutaneous injections) should therefore be pushed to the limit of tolerance in doses of 1 cc. per 10 pounds body weight twice weekly, or 30 cc. per week, for a patient of 150 lbs. as a minimum, and increased by at least fifty per cent. in acute or reacting cases, when improvement may be expected within three months. Some years' experience of this intensive treatment as compared with weekly injections of 1–5 cc. has shown much more marked improvement and much less incidence of

lepromatous change with the high doses. In lepromatous cases, reactions should be avoided, but dosage should be as high as possible short of producing increased erythrocyte sedimentation and plantar pain on heavy stroking. Surveys of school children are of great importance in finding the early macular stage and their discovery may lead to the detection of infective adults who require to be segregated. *L. Rogers*

Leprosy Review. 1948, Jan., v. 19, No. 1, 20–22. **Regional and Racial Differences in Leprosy.** A Report made from Statistics from Dr. C. J. Austin.

The Fiji Central Leprosy Hospital at Makogai provides both for the Melanesian population of various South Pacific islands and for Indian immigrants to the same region. The latter have a diet richer in protein, fat and vitamins than the indigenous people, whose diet is mainly carbohydrate. There is, however, a higher incidence of lepromatous cases among the Indians than in the Fijians and most of the other Islanders. No significant variations are attributable to climatic conditions. Yet in India there is a low incidence of lepromatous cases, and tuberculoid cases show much greater nerve enlargement as compared with Indian cases in the South Pacific, where the Indian group show a higher percentage of improved cases as compared with the Melanesian patients. Racial resistance therefore appears to show itself more in power to combat the disease than in preventing its onset. *L. Rogers*

Floch, H. & Camain, R. Sur la classification Sud-Américaine de la lèpre et son application en Guyane française. [**The South American Classification of Leprosy and its Application in French Guiana.**] *Institut Pasteur de la Guyane et du Territoire de l'Inini. Publication No. 153.* 1947, May, 11 pp.

Johansen, F. A. **Endemic Foci of Leprosy in the State of Texas.** *Internat. J. Leprosy.* Cleveland, Ohio. 1947, Oct.–Dec., v. 15, No. 4, 417–23.

This note deals with recent data on the incidence of leprosy in the Gulf States. In 1921, Boyd and Fox (*Amer. J. Pub. Health*, 1921, v. 11, 628) obtained data to show the occurrence of 45 cases during the previous thirty years; 36 of which were known to be of local origin, 5 were imported and the origin of 4 was unknown; most cases occurred among foreign-born Germans. Since 1921, 26 cases have been admitted from Galveston to the Louisiana leprosarium, 12 of German parentage; a number that does not include all. Brownsville is another endemic focus, from which 33 patients have been admitted; 42 others came from San Antonio and 22 from Houston. The total patients admitted in Texas since 1921 amounted to 231, 62 of whom have been discharged with the disease arrested. However, 137 were either born in Mexico or were of Mexican descent. The diseased should be separated from the healthy, especially from children. *L. Rogers*

Soeur Marie-Suzanne. Culture du bacille de Stefansky sur embryon de poulet. [**Culture of Stefansky's Bacillus on Chick Embryo.**] *C. R. Soc. Biol.* 1948, Jan., v. 142, Nos. 1/2, 35–6.

Manalang, C. **Criticisms against my New Orientations in the Etiology of Leprosy.** *Monthly Bull. Bureau of Health.* Manila. 1947, Jan., v. 23, No. 1, 5–18.

MANALANG, C. **Significance of Pathologic Findings in Biopsy Materials from Lepers. Part V.** *Monthly Bull. Bureau of Health.* Manila. 1947, Feb.–Mar., v. 23, No. 2, 85–91.

In this and the following paper the author reports further microscopical studies [see this *Bulletin*, 1932, v. 29, 545; 1936, v. 33, 607]. The title is also given of a third paper of a controversial nature.

The author reports on 75 microscopical examinations of the skin from 15 cases, 60 of which were from clinically normal skins. Only six were bacteriologically positive. Tuberculoid changes were met with in 10 normal patches of skin, variable degrees of perivascular round-cell infiltration in 40 (66 per cent.); only 10 of the clinically normal areas were histologically normal. He refers to the finding, in cases of ulnar nerve thickening, of very limited anaesthetic areas, sections of which showed signs of local disease. Histological changes in clinically normal skin bordering on a macule explain the frequency of relapses. He holds that such early histological changes precede the formation of lepromata, and that he has proved that large hazy macules on the face, trunk and extremities of child contacts of persons suffering from leprosy are the sites of future leprosy lesions, the result of infection in infancy through frequent and prolonged skin contact with the leper. *L. Rogers*

MANALANG, C. **Pathologic and Bacteriologic Survey of Lepers. VI. (Post Mortem.)** *Monthly Bull. Bureau of Health.* Manila. 1947, Feb.–Mar., v. 23, No. 2, 117–28.

In this article the author tabulates and discusses the histological findings in clinically normal skin of the hairy scalp and axillary fossae from forty-eight bodies examined post mortem in the Philippines. A table summarizing the results shows that in portions of skin from above the ears, the occiput and above the forehead, which often come in contact when a child is carried by a leprous mother, miliary leproma were found in 21·7 to 25 per cent., and *Myco. leprae* in 34·8 to 50 per cent. On the other hand, in skin from the forehead or axillae the comparable figures were only from 4·2 to 6·2 and from 17 to 28 per cent. respectively. The author attributes the high rate of alopecia leprotica in Japanese to the religious custom of shaving the head at the age of 100 days, and regards this as undeniable evidence of infantile infection. He maintains as a biological law that: "In leprosy, it is infantile infection with the leper's sweat and adult immunity." He regards the latter as complete and thinks that all infections occur in very young children. The rest of the two above papers are taken up in attempting to controvert findings of various authorities which are at variance with his hypothesis [see also this *Bulletin*, 1936, v. 33, 607].

L. Rogers

FERNANDEZ, J. M. M. & MERCAU, R. **Immunology of Leprosy. Antigens derived from *Mycobacterium leprae* in Oily Suspension.** *Internat. J. Leprosy.* Cleveland, Ohio. 1947, Oct.–Dec., v. 15, No. 4, 389–405, 13 figs. on 2 pls.

The authors were led to undertake this investigation by the finding of SAENZ and CANETTI (*Semana Médica*, 1941, v. 46, 3) that when killed tubercle bacilli were suspended in liquid paraffin, their toxicity was greatly increased on injection into guineapigs. Desiccated lepra bacilli separated from leprous tissues by Dharmendra's chloroform method and used in strength of 1 part in 5,000 of liquid paraffin, or in olive oil or in benzylic esters of chaulmoogra oil (neochaulmesterol) were employed as antigens; and as controls, heat-killed-typhoid bacilli in paraffin and the oily vehicles alone. All three types of leprosy were

used, together with healthy control subjects and the reactions to intradermal injections of the antigens were noted after 24, and 48 hours and at the third week for early and late appearances, illustrations of which are recorded. The results showed that the three oily suspensions of *Myco. leprae* antigens produced intense local reaction in 24 to 48 hours in all cases of leprosy, including the lepromatous type, but they were most intense in tuberculoid cases. As early reactions were as constant, although less severe, with oily suspensions of typhoid bacilli they are not considered to be specific. Control tests showed that the early reactions are not due to the oily vehicles used, so the intense reaction in tuberculoid cases indicates that action of *Myco. leprae* is increased in an oily suspension. The authors therefore think that the oily vehicle maintains contact of the bacilli with the dermis at the site of injection. Late reactions in tuberculoid cases were intense, with hard infiltration and sometimes ulceration. In lepromatous cases, a non-inflammatory nodule or plaque persisted, well localized and never ulcerating. In persons considered non-leprous, infiltrated nodules or plaques, with at times central areas of necrosis, were seen, but less intense than in tuberculoid forms. A further interesting observation was that in several lepromatous cases intradermal injection of the oily suspensions of *Myco. leprae* were followed after three to five months by positive reactions to standard lepromin, but this change in the allergic state lasted for only a short time, after which lepromin again gave negative results. This temporary sensitization to lepromin is being further studied. *L. Rogers*

DHARMENDRA. **The Lepromin Test—A Review.** *Leprosy Review.* 1947, Oct., v. 18, No. 4, 92–126, 1 coloured pl. [99 refs.]

This is in itself a comprehensive summary of the literature of the subject with full references and quotations of the most important data on its various aspects, from the first intracutaneous injections of lepra bacilli by MITSUDA in 1916. The advances made by HAYASHI in 1933, the suggestion of FERNANDEZ that the early and late reactions may be due to different antigens, and the explanation furnished by Dharmendra himself that protein constituents account for both reactions (the delayed one being due to slow breaking up of the injected whole dead lepra bacilli in the tissues) are well brought out. Findings are quoted which indicate that the test was of considerable value in classification of cases, and in prognosis, but little in diagnosis and treatment. Among matters regarding which there is still much difference of opinion may be mentioned; the significance of occasional reactions in healthy subjects and in contacts of infected cases; claims that repeated tests may increase the resisting powers of children to infection; stronger reactions in summer than in winter; variations in reactions in different skin areas; and the effect of debilitating conditions in reducing reactions; all of these require further investigation. A careful discussion on the nature of the reaction leads the author to the conclusion that a positive lepromin reaction is an allergic phenomenon. Another use of the test is to determine if a given acid-fast bacillus is that of leprosy or some other form; for infection of the latter give positive reactions in lepromatous as well as in other types of leprosy, which *Myco. leprae* does not. [This useful publication should be kept at hand for reference by all using the lepromin test, the results of which are illustrated by a coloured plate.] *L. Rogers*

IGNACIO, J. L. & TIONG, J. O. **Further Observations on the Mitsuda (Lepromin) Reaction in Leprous Children.** *Monthly Bull. Bureau of Health.* Manila. 1947, Feb.–Mar., v. 23, No. 2, 93–101.

This paper confirms the work of LARA [this *Bulletin*, 1940, v. 37, 632] on a tendency of young children to react more strongly to lepromin with increasing

age and with repeated tests. Three groups of children, amounting to a total of 216, were tested with lepromin ; the results are tabulated and discussed. The greater proportion of strong reactors in those tested several times, compared with those injected with lepromin only once or twice, is noteworthy. Direct relationship between repeated testing and clinical improvement or subsidence of leprotic lesions indicates a favourable influence of the lepromin in children and may indicate that lepromin has some immunizing value, especially when the subjects are of about the same age, but further work is required to establish such an effect. Further, in 31·5 per cent. of first injections the original lesions had apparently already healed, which indicates increased natural resistance after childhood, as is believed to be the case with tuberculous children. Strong reactions probably indicate a relatively high degree of resistance with a better prognosis, but the relationship is not constant. Children showing consistently weak reactions also have a poor prognosis, but they form a small minority of the cases. These observations confirm the prognostic value of lepromin reactions. *L. Rogers*

NOLASCO, J. O. **The Potency of Stored Lepromin.** *Monthly Bull. Bureau of Health.* Manila. 1947, Feb.–Mar., v. 23, No. 2, 103–14.

Quotations from medical literature show very varying opinions on the keeping powers of lepromin, so this paper is timely. The lepromin used in the present investigation was prepared by the technique of Hayashi, and was proved by microscopical examination to contain numerous well-preserved lepra bacilli, some in globi ; but as the number may vary much in different specimens, this method of preparation is capable of improvement. In the first series of tests, before the Japanese invasion of the Philippines, eight lepromins, which had been stored for 1 to 41 months in a refrigerator, were all injected in the forearms of twenty patients, and weekly observations were made up to the 28th day ; these are discussed in detail. Except for some minor variations in the reactions following the use of particular samples, all gave normal reactions with ultimate suppuration of the nodules at the sites of injection. In a second series, seven specimens kept throughout the war, with only very occasional refrigeration for a few hours, up to periods of 49 to 96 months, together with a control only 14 days old, were injected simultaneously in another group of twenty patients. Microscopical examinations showed undiminished numbers of lepra bacilli in all the specimens, and once more the reactions were typical. The author therefore concludes that lepromin prepared by the Hayashi-Mitsuda method keeps its properties undiminished for very long periods without any necessity for its being preserved in a refrigerator. *L. Rogers*

DE SOUZA LIMA, L. & DE SOUZA CAMPOS, N. **Lepra tuberculoide. Estudo clínico histopatológico.**

This book is reviewed on p. 658.

WOLCOTT, R. R. **Erythema Nodosum in Leprosy.** *Internat. J. Leprosy.* Cleveland, Ohio. 1947, Oct.–Dec., v. 15, No. 4, 380–88, 4 figs. (1 on pl.)

The author states that erythema nodosum occurring in leprosy is often confused with acute lepra reactions and he gives the following points of differentiation between the two conditions. Erythema nodosum differs from the acute lepra reaction in that its onset is less abrupt, the numerous evanescent discrete red nodules rarely show lepra bacilli, fever may be absent or intermittent, and without loss of weight and strength. Moreover, the lesions of erythema nodosum are painful on pressure, show vascular changes and are common under

sulphone treatment, during which lepra reactions are rare. Very numerous nodules may appear within a few hours, and fresh lesions may occur when the first have subsided. Oedema of the corium with swollen connective tissue fibres are found microscopically and the appearances indicate an antigen-antibody immune reaction. There is a close relationship to treatment, for only 7 per cent. occurred before treatment was begun, but they were more frequent under sulphone treatment and also of shorter duration and their appearance is considered to be a definite indication of the resistance of the host. Intramuscular injections of Fouadin in 3–5 cc. doses produced general improvement after a few days, and this allowed antileprous treatment to be continued without interruption in nearly all the cases, especially when sulphones were being used. *L. Rogers*

ROGERS, L. **Combined Chaulmoograte and Sulphone Treatment of Leprosy and Tuberculosis.** *Lancet.* 1948, Apr. 3, 515–17. [14 refs.]

LANCET. 1948, Apr. 3, 524. **Chemotherapy of Leprosy.**

Oral administration of chaulmoogra oil in the past was so nauseating that few leprous patients could be induced to persevere with it. Great advance, therefore, was made when its active constituent, sodium hydnocarpate, 'Alepol', which was given by injeotion, was substituted. The author, in 1916, demonstrated that subcutaneous injection of alepol led to the breaking up of the bacilli, sometimes with softening of nodules, and, later, that, when intravenously injected, it produced more rapid destruction of the bacilli and more rapid improvement in the lesions. But intravenous injections in advanced cases might result in long-continued fever and debility, although the clearing up of lesions might be remarkable. The author, therefore, proposed that injections should be given intramuscularly for some weeks and, when progress began to slow down, the intravenous route should be used for a few doses. The mode of action of the drug was found to be by its fat-splitting property and by breaking down the protective fatty envelope of the bacilli and rendering them vulnerable.

In recent years, sulphone preparations have been used in treatment of leprosy and favourably reported upon, especially Promin by FAGET *et al.* [this *Bulletin*, 1947, v. 44, 594] in the Carville leprosarium, and Promizole and Diasone by the same workers and by MUIR (*ibid.*, 326, 327]. The latter drugs have the advantage of oral administration, whereas the first must be injected. These drugs act by destroying the bacilli entering the blood-stream, so that fresh lesions by blood transmission are prevented.

The author has shown thus that the actions of chaulmoogra and these sulphones are complementary: the former destroying the bacilli in large numbers in the leprous lesions with the risk of surviving organisms being disseminated by the blood, whereas the latter destroy them when they reach the circulation. In order to ensure the presence of the bactericidal drug in the blood before pushing the chaulmoograte to the point of softening of the lesions and dispersion of organisms, it is recommended, says the author, that several weeks' treatment with one of the sulphones should precede the larger doses of chaulmoogra.

Analogies between *Myco. leprae* and *Myco. tuberculosis* have naturally led to the suggestion of using sodium hydnocarpate and morrhuate in tuberculosis, and success has followed the use of colloidal copper morrhuate, *Gadusan*, in this disease; the author suggests that trial should be made of this "in combination with sulphones or with streptomycin in tuberculosis on the same principles as in leprosy."

A leading article on this subject points out that the actual evidence of chaulmoogra preparations being bacteriolytic is not strong and that their effect may be due to counter-irritation and the stimulation of a tissue response. The article also refers to untoward and possibly dangerous side-effects of treatment with sulphones, such as gastro-intestinal disturbance, haemolytic anaemia, haematuria and even agranulocytosis. It is suggested, further, that *p*-aminosalicylic acid, which seems to have some specific action on acid-fast bacilli, has low toxicity and has been tried in tuberculosis, might, when it is more readily available, be given a trial in leprosy. *H. Harold Scott*

FAGET, G. H. & ERICKSON, P. T. **Chemotherapy of Leprosy.** *J. Amer. Med. Ass.* 1948, Feb. 14, v. 136, No. 7, 451–6, 6 figs. [Refs. in footnotes.]

This paper records the latest observations on the sulphone treatment of leprosy. This group of drugs has now been under trial in lepromatous cases at the Carville Settlement, U.S.A., for six years, almost entirely with better results than any former treatment. Promin on account of its toxicity has to be given intravenously in doses gradually increased from 1 to 5 gm. daily for two weeks at a time, with one week's interval at the end of each fortnight. Diasone is given orally beginning with 0·3 gm. in a capsule or as a tablet daily, and increased if well tolerated to two or three such doses daily, with periods of two weeks' rest after every two months' treatment. Promizole is given orally, 0·5 to 1 gm. three times daily and gradually increased to the optimum dose of 6 to 8 gm. a day. No renal damage was found from any of them under the carefully controlled conditions of medication, but careful watch must be kept for anaemia or leucopenia, which may require temporary cessation of the treatment and the use of iron or liver therapy.

Most of the patients treated had advanced lepromatous disease ; notes and illustrations before and after treatment of three cases show striking improvement, Progress is seldom evident in less than six months and is very slow, but steady. with very few relapses and is in proportion to the duration of treatment. Promin and diasone give very similar results. Of the patients treated, 25 per cent. show improvement after six months, 60 per cent. after one year, 75 per cent. after two years and almost 100 per cent. after three years' treatment. It is shown by slow shrinking and absorption of nodules until only a pigmented scar may remain, ulcers develop healthy granulations and heal and there may be some regrowth of hair. Mucous lesions respond better than cutaneous lesions. The progress of eye lesions is checked, with occasional improvement of vision. The frequency and severity of reactions are reduced. Lepra bacilli in the lesions gradually become less numerous and after four years they disappear in over 50 per cent. Those entering the blood stream are eliminated and the development of fresh lesions is prevented. The histological changes in lesions are of an atrophic nature. The proportion of cases in which the disease is arrested under prolonged promin and diasone treatment is 8·3 per cent. in 1–2 years, increasing to 21 to 29 per cent. after three to six years.

Antibiotics have also been tried in leprosy, but penicillin is only of use in secondary infections of ulcers. Streptomycin has given encouraging results, but they are not as yet conclusively demonstrated and require further tests.

In a discussion on the above paper, H. M. Johnson of Honolulu reported encouraging results in Hawaii from the use of promin and diasone. *L. Rogers*

JOHANSEN, F. A. & ERICKSON, P. T. **Promizole Treatment of Leprosy. (A Progress Report).** *Internat. J. Leprosy*. Cleveland, Ohio. 1947, Oct.–Dec., v. 15, No. 4, 378–9.

This note records a trial lasting two and a half years of Promizole in leprosy at the Carville Leprosarium, U.S.A. It was found to be slightly less toxic than

the other sulphones, but does not appear to have any other advantages. It is given orally in doses six to eight times as great as those of promin or diasone, and becomes distasteful and unpalatable. It also produces a harmless cherry-red colour of the urine. It is synthetized with difficulty and is expensive. Treatment was started on 25 patients, who have fallen to 15, of whom 7 have been under treatment for 2½ years, but two of these are now using other preparations. Two of the patients have become negative bacteriologically and clinical improvement continues to take place. Of 5 patients treated for only one year, all are still bacteriologically positive. Three of the patients have died of intercurrent diseases. In view of these drawbacks it is not proposed to continue the trials after the present supplies of promizole are exhausted.

L. Rogers

DE MESQUITA, A. P. **Seabra's Photo-Oxidasic Test in Leprosy.** *Med. Times.* New York. 1948, Feb., v. 76, No. 2, 56–60, 73, 4 figs.

This paper describes a new prognostic test of a technical nature. Seabra has studied oxidases and worked out an index for them in the leucocytes, which varies with barometric pressure, and a photo-oxidase test for measuring them. The erythrocyte oxidase falls in tuberculous subjects, and this is due to " Factor P " secreted by tubercle bacilli inactivating the lipase produced by the lymphocytes. Seabra also found a similar drop in erythrocyte oxidase in a few cases of leprosy. This test has now been applied in 100 leprosy cases, with the result that the lowest readings are found in the more serious cases with the worst prognosis, mainly lepromatous disease, in which it is below the normal limit of 40. In nerve cases, classed by the South American nomenclature as " uncharacteristic " and tuberculoid, on the other hand, the readings are usually above 40. Thus among 67 lepromatous cases, Seabra's photo-oxidasic tests showed low figures in 53 (79 per cent.). Of 14 cases without low readings, 6 have greatly improved and 8 have become free of cutaneous signs. The nerve types revealed normal readings over 40 in 25 of 33 cases (75·76 per cent.), and several of the exceptions were not doing well. A table and illustration show the readings in the 100 cases. For technical details, the original should be consulted.

L. Rogers

HELMINTHIASIS

THURET, C. & THIBAULT, C. *Bacillus bifidus* dans la lutte contre les helminthes intestinaux de la souris. [*Bacillus bifidus* **as an Antagonist to Intestinal Helminths in Mice.**] *C. R. Soc. Biol.* 1948, Jan., v. 142, Nos. 1/2, 44–6, 2 graphs.

The following is a translation of the author's summary.

The use of a culture of *Bacillus bifidus* in the form of washings provides a powerful weapon against intestinal helminths in mice and is completely innocuous for the host. A hope is expressed that it will be possible to bring it into general use in human and veterinary medicine.

H. J. O'D. Burke-Gaffney

i. KREIS, H. A. Eine systematische Bemerkung zur Arbeit: H. Vogel und W. Minning: Ueber die Einwirkung von Brechweinstein, Fuadin und Emetin auf Bilharzia japonica und deren Eier im Kaninchenversuch. [**Comment on the Paper by Vogel and Minning on "The Action in Rabbits of Tartar Emetic, Fouadin and Emetine on** *Schistosoma japonicum* **and its Eggs."**] *Acta Tropica.* Basle. 1947, v. 4, No. 3, 259–60.

ii. ——. Bilharzia oder Schistosoma? Ergänzende Mitteilung zur Bemerkung *H. A. Kreis* in Acta Tropica Vol. 4, 259–260, 1947. [*Bilharzia* **or** *Schistosoma?* **Further Communication.**] *Ibid.* 1948, v. 5, No. 1, 87–8.

i. VOGEL and MINNING's paper was abstracted in this *Bulletin* [1948, v. 45, 196] and the author of this comment does not criticize the work which he says is of much interest, but he objects to the name of the trematode. He traces historically the changes in the naming of this worm. Bilharz describing it in 1852 called it *Distomum haematobium.* Six years later, Weinland stated that it did not belong to this genus *Distomum* and put it under a new genus *Schistosoma,* and *Schistosoma haematobium* (Bilharz, 1852) became *S. haematobium* Weinland, 1858. But in the same year, Diesing gave it the generic name of *Gynaecophorus* and in 1859 Cobbold, in honour of its discoverer, called it *Bilharzia* and the same year Moquin-Tandon called the new genus *Thecosoma.* The author argues that as Weinland was the first to show that it did not belong to the genus *Distomum,* according to the laws of nomenclature its correct name is *Schistosoma.* VOGEL and MINNING, however, called the helminth they were dealing with *Bilharzia japonica* on the ground that Meckel used the term *Bilharzia* in 1856, or two years before Weinland created the genus *Schistosoma.* LEUCKART in his work on *Die Parasiten des Menschen* calls the urinary schistosome "*Bilharzia* Cobbold, 1859" which is certainly wrong if Meckel had called it so three years before. So far, all seems plain sailing, but prolonged search has failed to find where Meckel called it *Bilharzia,* and the works of Lutz, of Faust, of Worth, Martin, Hunter and others say nothing about Meckel. Therefore, until proof is obtained that Meckel *did* make the genus *Bilharzia* in 1856, the name *Schistosoma* Weinland, 1858 must hold good.

ii. In his supplementary note Kreis dwells on the fact that in the account of SENN's booklet on Theodor Bilharz, Professor Leiper speaks of a posthumous work "Mikrogeologie" by Meckel von Hemsbach, published in 1856, in which the generic name *Bilharzia* is used. Meckel as the originator of the name *Bilharzia* is also mentioned in a book on *Famous Tropical Physicians* by G. OLPP, published in Munich in 1932. In Professor Leiper's words: "Those who regretted the displacement of the generic name *Bilharzia* Cobbold, 1859 by *Schistosoma* Weinland, 1858 under the Law of Priority will rejoice in the restoration of *Bilharzia* Meckel, 1856 under the same Law." [See this *Bulletin,* 1932, v. 29, 168.] In spite of, or in comment on, this, E. W. PRICE (*J. Parasitology,* 1933–4, v. 20, 111) wrote: "but in this case priority is of little moment in view of the fact that in 1922 *Schistosoma* was placed on the list of official names under Opinion 77 of the International Commission on Zoological Nomenclature." To end the dilemma, Dr. Kreis in 1938 asked the Commission for a decision and he received a reply from the President saying that he would bring the request to the notice of the members; he suggested that in the meantime as *Bilharzia* could obviously claim priority, this name should be used and provisionally *Schistosoma* should be inserted in brackets. Dr. Kreis says that he repeated his request in 1947, but, so far as he knows, no decision has yet been made. He adds naively, "When the decision is reached, it will be authoritative."

H. Harold Scott

RANSFORD, O. N. **Schistosomiasis in the Kota Kota District of Nyasaland** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 617–28, 1 map. [20 refs.]

Schistosomaisis is common in Nyasaland. At the Kota Kota hospital, on the lake shore, 53 per cent. of 9,861 urines examined in the period 1935–44 contained eggs of *S. haematobium*; the incidence of *S. mansoni* eggs in 13,090 specimens of faeces examined declined from 7 per cent. in 1935 to 1 per cent. in 1944. The author argues that this reduction in the detected incidence of *S. mansoni* is a result of improvements in sanitation. [This may be so, but on the evidence presented it is impossible to be sure that there was no change in the selection of patients for stool examination; thus, if stools have recently been examined on slighter suspicion than before, a lower proportion of positives would be expected.]

The author examined the urine of 1,857 children at various places in the district, and found eggs of *S. haematobium* in 51 per cent.; in boys 58 per cent., and in girls 49 per cent. were affected. In no case was infection found in a child of less than 4 years of age. The greatest incidence was in children from the lake shore area, and incidence decreased with altitude. In Kota Kota itself, 81 per cent. of children examined were infected.

Only one snail, *Physopsis globosa*, was constantly found in association with foci of *S. haematobium* infection, and in 1,200 dissections of possible snail hosts, only this species was found to harbour cercariae resembling those of *S. haematobium*. Experimental proof was obtained that this snail could act as host. Other snails found included *Bulinus forskali, Lymnaea caillaudi, Biomphalaria pfeifferi* and *Melanoides tuberculata*, but although the first two may act as emergency hosts, the author thinks that they can do so only rarely. *P. globosa* is found in great numbers in residual pools near human habitations (but rarely in pools in uninhabited areas) and also in rice fields during the rains; it seems that this snail requires fouling of its habitat. Pools gradually dry up as the dry season continues, and become progressively more foul as they are more used. Backwaters of lake water are not important sources of infection, and the lake itself is safe.

The only hope of permanent control is to eliminate village pools close to the lake, by drainage, filling, or diversion and utilization of the water in deep wells. The author, however, discusses the use of substances to poison the snails, and commends especially the leaves of *Tephrosia vogelii*, which can be cultivated easily and cheaply, and which can be used until the more permanent measures become effective. It is commonly used as a fish poison, and the people are accustomed to handling it. The leaves may be crushed, or merely torn by hand, and they may be fresh or dry; a concentration of 1 in 2,000 or 1 in 3,000 [presumably weight/volume] will kill snails in 24–48 hours, even if there is mud or scum. Volunteers who drank ½ pint of 1 in 2,000 extract suffered no ill effects. The active principle is allied to rotenone. *Charles Wilcocks*

DE MAGALHÃES, O. & ROCHA, A. Estudos sôbre a doença de Manson-Pirajá. (Esquistosomose pelo "Schistosoma Mansoni"). [**Studies on** *Schistosoma mansoni* **Infestation.**] *Mem. Inst. Oswaldo Cruz.* 1947, Mar., v. 45, No. 1, 183–210. 7 figs. & 2 maps. [Bibliography.] English summary.

This is an account of infestation by *Schistosoma mansoni* as it occurs in the State of Minas Gerais, Brazil. TEIXEIRA in 1920–21 examined the faeces of nearly 10,000 persons in Belo Horizonte and found 4·9 per 1,000 positive. It was consequently thought that this infestation was not serious in Minas Gerais. In 1933, however, one of the authors examining the question afresh found that the incidence was greater and in 1935 reported the fact to his colleagues and

by 1937 the incidence was found to have increased more than tenfold, to 5·69 per cent. and soon after to 11·79 per cent., owing, it was said, to the opening of baths in Pampulha. Then, in 1940–42, examinations of a more detailed character discovered the presence of ova in the ileum, caecum, rectum, liver, spleen, lungs, ovaries, testicles, bladder, etc., causing proctitis, colitis, appendicitis, hepatic cirrhosis, " pseudo-tuberculosis " of lungs and intestine, and not a few surgical conditions are now known to be associated with *S. mansoni*, such as rectal polyp, stenosis of rectum, perirectal abscess, fistulas, vulval tumours and chronic appendicitis.

An interesting map accompanies this article showing the widespread distribution of the worm in the State. Thirty-eight towns were investigated and 17 of them were found infested with this trematode, and all 38 showed helminthiasis of some kind. Of 4,176 samples of faeces, 90·4 per cent. were positive for one or other and 6·6 per cent. positive for *S. mansoni*. In Sabará, 66 per cent. of those of school age (12–16 years) were positive and 50·7 per cent. of all those examined. Other percentages were : Ibirité 26·9, Ponte Nova 22·3, Ubá 16·5 and Belo Horizonte 14·5. There should be established, say the authors, a National Anti-Schistosomiasis Service in Brazil. *H. Harold Scott*

Noya Benitez, J. **Splenectomy in Schistosomiasis. Preliminary Report.** *Puerto Rico J. Pub. Health & Trop. Med.* 1947, Dec., v. 23, No. 2, 247–55. [Refs. in footnotes.] [Spanish version 256–65.]

The typical Banti's syndrome following a schistosomal infection is associated with portal hypertension, the result of intrahepatic portal obstruction due to cirrhosis caused by ova of the parasites. This condition may occur even when the schistosomal infection is adequately treated, and death from haematemesis may occur before it fully develops. Splenectomy, although neither as radical nor mechanically as efficient as spleno-renal or portacaval anastomosis if successfully established, should relieve the portal hypertension and lessen the tendency to bleeding from oesophageal varices.

After a review of the literature on these various procedures, the author decided that splenectomy is justifiable if performed early, and before the liver damage is excessive and there is ascites. Under these conditions the risk of operative and post-operative mortality is reduced. He performed 20 splenectomies in a period of 18 months ; the youngest patient was 15 years and the oldest 41 years ; 17 of the patients were between 16 years and 30 years. All came from the schistosomiasis-endemic area of Porto Rico, and all had been treated with antimony for bilharzia ; in none did the faeces still contain ova of *Schistosoma mansoni*, although these had previously been found. In one case only, eggs were recovered by rectal biopsy. Ten of the patients had had haematemesis, and 15 had had melaena. The spleens removed ranged in weight from 500 to 2,220 gm. The longest follow-up period was 20 months, the shortest four weeks. There was no operative or post-operative mortality within the periods of observation. Data are given in tables of the pre-operative and the post-operative findings in each case. Haematemesis recurred post-operatively in three patients ; all survived. The general health and condition of all the patients improved after operation. The author therefore recommends splenectomy as the treatment of choice for Banti's syndrome due to schistosomiasis.
A. R. D. Adams

Ross, W. F. **Acriflavine in the Treatment of Schistosomiasis.** [Correspondence.] *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 685–6.

The writer of this letter refers to the experiences of Fisher with acriflavine in the treatment of intestinal schistosomiasis in the Belgian Congo [this *Bulletin*, 1935, v. 32, 239].

The present author with BLAIR treated seven patients with acriflavine in Salisbury, Southern Rhodesia: all suffered from *S. haematobium* infections and three had *S. mansoni* as well. The patients were adolescent school children and all were passing viable eggs. They were given the dose quoted by Fisher, namely a total of 0·01 gm. per kgm. body weight in five equal daily doses of 2 per cent. acriflavine. No evidence of toxicity was noted.

At the end of treatment, one patient with *S. haematobium* had ceased to pass viable eggs, and remained negative for the further period of two months follow-up. One month after treatment, a patient who had *S. mansoni* was negative, but showed eggs again after 2 months.

It is pointed out that most of Fisher's cases had become negative immediately after treatment and that, unlike the present instance, his cases comprised solely intestinal schistosomiasis.

In the present author's small series of cases of vesical schistosomiasis, the effect of acriflavine was found to be almost negligible.

H. J. O'D. Burke-Gaffney

SCHUBERT, M. **Conditions for Drug Testing in Experimental Schistosomiasis mansoni in Mice.** *Amer. J. Trop. Med.* 1948, Jan., v. 28, No. 1, 121–36, 4 figs. [17 refs.]

An investigation is described to find the best method for testing drugs on experimental schistosomiasis. A number of points are involved (1) The species of schistosome and its intermediate host. *S. mansoni* and *Australorbis glabratus* were convenient and satisfactory. *S. haematobium* would develop well in mice, but it was difficult to obtain any large number of cercariae from *Bulinus truncatus*. *S. japonicum* was not available. (2) The animal host chosen was the mouse. Hamsters develop infections more readily, but are less easy to use for screening drugs. Rabbits are convenient if large numbers of adult worms are required. Rats are not very susceptible to infection, and are unsatisfactory. (3) The mice were infected by intraperitoneal injection of a standard number of cercariae. This was more convenient and uniform than immersing them in water containing cercariae. (4) The optimum number of cercariae per mouse was 100–150; when this number is injected intraperitoneally, about 9 per cent. develop into adult worms and 90 per cent. of the mice are infected. Higher doses of cercariae kill too many of the mice. (5) Even with a standard dose of cercariae the number of worms which develop in the mice varies considerably; in groups of 15 mice, there may be 5 or 20 worms in individual mice. (6) The infection in the mice becomes mature, *i.e.* eggs are passed, during the sixth or seventh week after infection; treatment was therefore begun during the eighth week. There was no evidence of spontaneous cure of the mice during the first 36 weeks. (7) The drug was given daily for two weeks, usually by intraperitoneal injection. If the drug was insoluble it was injected as a suspension or given in the diet. (8) The criterion of cure. Even after treatment with Fouadin or sodium antimony tartrate, few of the mice become completely free from worms. Accordingly, the effect may be judged by the location of the worms (antimonials drive them from the mesenteric veins into the liver), and by the percentage of worms paired (diminished by antimonials). The presence or absence of viable eggs in the faeces was found to be very variable, even in untreated mice. (9) During the first two weeks after treatment, worms which have been driven into the liver, but not killed, may recover and reascend the mesenteric veins and begin to lay eggs again. Accordingly, the mice should be held for two weeks after treatment and then killed; and the number and location of the worms should be compared with those of control untreated mice. Usually 10–15 mice are used in a group. [The

author seems to have had more difficulty in demonstrating the helminthicidal action of active drugs than KIKUTH and GÖNNERT did in Germany ; the latter workers have used a similar technique since 1936 and judged the response according to the passage of eggs and the presence or absence of living worms at autopsy 4 weeks after treatment.] *F. Hawking*

SCHUBERT, M. **Screening of Drugs in Experimental Schistosomiasis mansoni in Mice.** *Amer. J. Trop. Med.* 1948, Jan., v. 28, No. 1, 137–56.

By means of the methods described above, over 400 compounds were tested, the names of these being given in lists. According to their therapeutic effects the drugs may be divided into four categories :—

(1) Drugs which cured most of the mice, *viz.* antimony tri(2. naphthylethyl mercaptide), antimony tri(n-dodecyl-mercaptide), and n-butyl 3,4 antimonyl gallate.

(2) Drugs which killed some of the worms, *viz.* Fouadin, antimony trithioglycollamide, antimonyl 2 mercaptothiazoline, antimony tri (2 mercaptoimiazoline), antimony tri (n-decylmercaptide), neostibosan, neostam, phenyl mercuric gluconate, emetine, miracil.

(3) Drugs which had only a slight action, *viz.* sodium antimony tartrate and 32 other compounds.

(4) Drugs with no action.

It should be noted that the pentavalent antimonials, neostibosan and neostam, both showed considerable activity and they probably deserve further clinical trials in the treatment of schistosomiasis. Antimony compounds soluble in oil also seemed worth further clinical investigation. Miracil was found to have considerable action when given in the maximum tolerated dose by injection or by mouth and it is said to deserve further investigation ; however it was not so effective in the author's animals as it was in those of KIKUTH and GÖNNERT. [This paper contains numerous data of great interest to those concerned in the search for new active compounds and should be consulted in the original.] *F. Hawking*

SCHUBERT, M. **Effect of Drugs during Earliest Stages of Experimental Schistosomiasis mansoni in Mice.** *Amer. J. Trop. Med.* 1948, Jan., v. 28, No. 1, 157–62.

Mice were infected with *S. mansoni* by the technique described above. On the first five days after intraperitoneal injection of the cercariae they were treated with daily doses of drug by intraperitoneal injection, or the drug was given in the food. The purpose was to prevent the development of the infection. The mice were killed and examined after eight weeks. Eighty drugs were tested in this way. Seven showed significant protective action, *viz.* antimony tri(2 naphthyl ethyl mercaptide), Fouadin, antimony tri (n-dodecyl mercaptide), neostam, neostibosan, urea stibamine and sodium antimony tartrate (in order of decreasing activity). The doses used were approximately the maximum tolerated ones. Miracil showed very little activity.

F. Hawking

KUNTZ, R. E., STIREWALT, M. A. & BUCHHEIT, J. R. **Method for testing Ointments and Fabrics to determine their Effectiveness as Barriers to Schistosome Cercariae.** *Amer. J. Trop. Med.* 1947, Nov., v. 27, No. 6, 691–7, 4 figs. [11 refs.]

Control of schistosomiasis in war may be attempted by destruction of the snail hosts (only moderately successful hitherto), temporary elimination of

cercariae by cercaricidal substances, or by protection of the skin by the use of uniforms made from protective fabric, or the use of repellents or barrier substances. In tests on animals, estimation of the penetrating power of cercariae by keeping the animals for 15–40 days and then dissecting them and counting the parasites which have developed is cumbersome, and the authors have devised a shorter test, which is probably sufficiently accurate. It is based on the observed fact that cercariae of *Schistosomatium douthitti* and *Schistosoma mansoni* penetrate hamsters and white mice with equal facility, and are affected to about the same extent by barrier substances. These animals show skin reactions when the cercariae have penetrated, but certain white rabbits about 6 months old constantly show much more prominent reactions to cercariae of *S. douthitti*, which render assessment of invasion much easier. It can be assumed, therefore, that the skin reaction due to *S. douthitti* is a reasonably accurate index of the invasive powers of equal numbers of cercariae of *S. mansoni* under the same conditions [but the authors do not prove that what is true of hamsters and mice is necessarily true of rabbits].

The authors describe a rubber belt, containing four test chambers of glass tubing 1 inch in diameter, which is applied to the skin of the belly of the rabbit. Into these chambers about 25 cercariae are introduced and left for ½ hour (with clothing barriers 50 cercariae are left for 1 hour), and the numbers of inflamed spots caused are counted every 4–8 hours for 2 days. The barrier ointments are placed on the skin before the cercariae are applied, but the fabrics are placed 1–3 mm. from the skin, and the intervening space is filled with water ; the cercariae are placed outside the fabrics.

For details of these procedures the original must be consulted. No results of actual tests are given. According to the list of references, most of the work done on fabrics and barrier substances has been recorded in official reports.

Charles Wilcocks

PESIGAN, T. P. **The Endemicity of Schistosomiasis japonica in Sorsogon, Southeastern Luzon.** *J. Philippine Med. Ass.* 1948, Jan., v. 24, No. 1, 19–27, 1 fig. & 1 map on pl.

The known endemic foci of *S. japonicum* infection in the Philippine Islands are Eastern Leyte, Samar, Surigao and Agusan, especially around Lake Mainit, and Mindoro, near Lake Naujan ; another focus has recently been found in Western Lanao [see this *Bulletin*, 1947, v. 44, 832]. The author has now confirmed a newly discovered endemic area in Sorsogon, Luzon. He had observed a few patients in the Philippine General Hospital, who came from Sorsogon, and he therefore made a survey in that area, finding 25 infected persons, most of whom had never left the district. A few of these persons were unaware of any serious illness, but in 16 the liver was enlarged, and distension of the superficial abdominal veins was found in 7. No less than 6 had had epileptiform attacks, but this should not be regarded as indicating the proportion so affected, since these patients were examined for schistosomiasis because they gave this history.

Search for snails revealed *Oncomelania quadrasi* in three streams, out of many investigated ; none of the snails was infected, but there is little doubt that this species, well known as the intermediate host elsewhere, is responsible for spread here.

In addition to schistosomiasis, the author found other infestations in 113 of 114 persons examined, including paragonimiasis and balantidiasis in one boy.

Charles Wilcocks

JAHNES, W. G. & HODGES, E. P. **An Improved Method of sedimenting *Schistosoma japonicum* and other Helminth Ova.** *J. Parasitology.* 1947, Dec., v. 33, No. 6, 483–6. [15 refs.]

The authors tested a number of chemicals and reagents in a search for the most effective method of sedimenting eggs of *S. japonicum*. A control method of evaluating the tests consisted in the use of 0·5 per cent. of glycerine in tap water. Of all the materials employed, 10 per cent. ethyl alcohol (sp. gr. 0·986) gave the best results, with the highest egg counts and no distortion. The procedure is as follows: 5 gm. of stool are emulsified, strained through four layers of moistened gauze and allowed to sediment for 1 hour, 45 minutes and 30 minutes successively, decanting at each time interval and replacing with fresh solution. After the final sedimentation, 0·15 cc. are taken from the top and bottom of the residual sediment, respectively, and examined.

J. J. C. Buckley

HUNTER, G. W., HODGES, E. P., JAHNES, W. G., DIAMOND, L. S. & INGALLS, J. W., Jr. **Studies on Schistosomiasis. II. Summary of Further Studies on Methods of Recovering Eggs of *S. japonicum* from Stools.** *Bull. U.S. Army Med. Dept.* 1948, Feb., v. 8, No. 2, 128–31, 2 figs. [Refs. in footnotes.]

Previous studies described evaluation of the various laboratory methods available for diagnosing *S. japonicum* infection [this *Bulletin*, 1947, v. 44, 440]. The present paper makes further comparisons and indicates that two new methods have shown themselves to be superior to all others in current use.

In the comparisons, qualitative and semi-quantitative estimations were made of 10 techniques, with the use of stools of dogs infected with *S. japonicum*, naturally infected human stools and those of monkeys infected with *S. mansoni*. The techniques were (1) direct smear, (2) sedimentation, (3) hydrochloric acid, Triton NE, ether centrifugation, (4) hydrochloric acid, sodium sulphate, Triton NE, ether centrifugation (AMS I method), (5) centrifugal sedimentation, (6) sodium sulphate Triton NE, ether centrifugation, (7) hydrochloric acid, ether, xylol, (8) funnel centrifugation, (9) AMS II method, (10) a modification now reported as the AMS III method.

The AMS I technique was a modification of the Telemann hydrochloric acid and ether method, as used by WELLER and DAMMIN [this *Bulletin*, 1947, v. 44, 98] except that the hydrochloric acid was mixed with equal parts of sodium sulphate. The AMS II method modified the AMS I technique by using 2 gm. of stool, by washing with water centrifugation before the HCl, sodium sulphate Triton NE, ether centrifugation technique and by swabbing out the tube before decanting the final residue on to a slide. The AMS III method substitutes washing 3 times with the HCl and sodium sulphate mixture instead of water before treatment by the HCl, sodium sulphate, Triton NE ether technique. The last named method is described in detail in the text. It requires less than 15 minutes. A total of 37 qualitative and 15 semi-quantitative comparisons were made. In every case, the AMS II and III proved to be the most satisfactory. The results are shown in two figures, which demonstrate strikingly the superiority of these two methods and particularly of the AMS III. Not only are more eggs revealed, but the slides are washed cleaner and are therefore comparatively easy to read.

It is added that the AMS III technique also appears to be efficacious for the detection of other helminths, and has the advantage of detecting *S. japonicum* eggs whether they are immature, mature or degenerate. It can also be used satisfactorily in examining stools of those who have already been treated.

H. J. O'D. Burke-Gaffney

HUNT, W. E., ABRAMSON, W. & WEAVER, T. A., JR. **Cerebral Schistosomiasis. Report of a Case simulating Cerebral Neoplasm.** *J. Amer. Med. Ass.* 1948, Mar. 6, v. 136, No. 10, 686–9, 6 figs. [Refs. in footnotes.]

A white labourer, aged 35 years, served with the army in Leyte, where he bathed in proscribed fresh water streams. In the United States, in September 1946, he began to suffer from transient loss of motor and sensory function on the left side of the body, and right-sided headache ; on one occasion he lost consciousness during an attack. Changes in his personality were noticed by his wife. In November 1946 a diagnosis of brain tumour was made after electroencephalographic and ventriculographic examinations. At operation, scattered white miliary nodules were seen on the right cerebral convolutions ; in the posterior portion of the inferior frontal gyrus there was a nodule, about 5 mm. in diameter, which was removed. On section schistosome ova, surrounded by lymphocytes and eosinophiles, were found lying in an area of connective tissue proliferation containing Langhans-type giant cells. Repeated stool examinations, sigmoidoscopic scrapings, and urine examinations failed to yield schistosome ova, but the patient was put on a course of antimony potassium tartrate. He made a good recovery, but there was some residual weakness of the left arm and he suffered an abortive sensory seizure some five months after the operation and treatment. [See also this *Bulletin*, 1947, v. 44, 916.] *A. R. D. Adams*

CARROLL, D. & HUNNINEN, A. V. **Studies on Schistosomiasis japonica in the Philippine Islands. 3. A Clinical Study of 72 Cases treated with Tartar Emetic.** *Bull. Johns Hopkins Hosp.* 1948, Mar., v. 82, No. 3, 366–72.

The treatment of *S. japonicum* infections on Leyte in 1944–45 with Fouadin has already been reported [this *Bulletin*, 1947, v. 44, 834]. The present report deals with 72 patients treated with tartar emetic, 32 of whom were followed into their seventh month of illness.

All cases were primary infections in hitherto unexposed American soldiers. The incubation period averaged 50·2 days for 68 cases. Five cases were classified as severe, 31 as moderately severe, 32 as mild and 4 as asymptomatic.

In treatment, 1·89 gm. of tartar emetic was used. The stock solution was 0·4 gm. of the drug per 100 cc. of 5 per cent. dextrose in normal saline ; the solution was not heated and was used within 3 hours of being mixed.

The solution was given in graded doses intravenously every other day for 18 doses, namely : 1st dose, 0·020 gm. of tartar emetic (5 cc. of solution), 2nd, 0·040 gm., 3rd, 0·060 gm., 4th, 0·090 gm. and, after the fourth dose, 0·120 gm. (30 cc. of solution) for all further doses.

In the first four doses the solution was diluted with the dextrose-saline to make 30 cc. of liquid injected. Injection was made into the antecubital vein over a period of about 10 minutes. Early minor reactions were cough, nausea and vomiting, while in some patients stiffness of the joints developed later as more of the drug was given. A chart indicates that there were many minor reactions : also in four cases, tartar emetic had to be discontinued owing to purpura ; substernal pain ; vascular collapse ; and cough with diarrhoea and vomiting, respectively. One month after the course of tartar emetic was completed, 32 patients were retreated with 40 cc. of Fouadin, owing to the presence of degenerated eggs in their stools. The Fouadin was given intramuscularly in doses of 5 cc. daily for 8 days.

All patients were discharged after 1 to 4 months : few of them felt completely well, although they carried on light duty. Of 31 patients weighed 7 months later, 35 per cent. had lost weight. There was no striking clinical

improvement with the institution of tartar emetic therapy. After the third month, glandular enlargement was no longer appreciable, and the spleen and liver tended to remain palpable in only a minority of the patients. These features are shown in a chart.

Tabulated figures for leucocyte and eosinophile counts are given: as time passed, these counts approached normal. Sedimentation rates of 29 patients in the 7th month were normal.

Two of the patients showed mature *S. japonicum* eggs in the 16th week after tartar emetic treatment and 2 in the 17th week. Three of these 4 had been retreated with Fouadin.

In 8 of 32 patients in the 7th month, sigmoidoscopy showed nodules in the rectum or sigmoid. Only one of these had a positive stool and 4 had been retreated with Fouadin.

The authors found no significant difference between the cases which recurred and those which did not in regard to the original leucocytosis and eosinophilia or for these values at the end of seven months. Retreatment with Fouadin was not effective in preventing recurrences. None of the asymptomatic cases recurred. The impression was gained that patients having tartar emetic had fewer recurrences than a comparable group treated with Fouadin alone [*loc. cit.*]. *H. J. O'D. Burke-Gaffney*

Douglas, D. M. **Hydatid Disease.** *Edinburgh Med. J.* 1948, Feb., v. 55, No. 2, 78–91, 4 figs.

A general account with special reference to experience in Iraq.

Hobson, A. D. **The Physiology and Cultivation in Artificial Media of Nematodes Parasitic in the Alimentary Tract of Animals.** *Parasitology.* 1948, Feb., v. 38, No. 4, 183–227. [Numerous refs.]

This is a detailed review of current knowledge of the physiology of the parasitic stages of nematode parasites in animals with particular reference to those species which are found in the alimentary canal; and of attempts which have been made to keep adult and larval phases of parasitic nematodes alive *in vitro*.

The review is a very useful work for anyone interested in the subjects or about to undertake research in them, but of no immediate value to human medicine. *J. J. C. Buckley*

Khoo, F. Y. & Chiang, H.-S. **Hookworm Disease showing Abnormal Roentgenologic Small Intestine Changes. Three Case Reports.** *Chinese Med. J.* Shanghai. 1947, Sept.–Oct., v. 65, Nos. 9/10, 349–56, 4 figs. on 2 pls.

Since Mackie [*Med. Clin. North America*, 1933, v. 17, 165] drew attention to the radiological changes in the small intestine in non-tropical sprue, considerable attention has been paid to the radiological picture in tropical gastro-intestinal disorders and malnutritional states.

Golden has divided these changes into two main classes,

(i) Changes in motility; hyper- and hypo-motility and -tonicity, abnormal segmentation, scattering effect, and gas and fluid levels, and

(ii) Changes in the mucous membrane:—exaggeration or obliteration of the mucosal folds.

These changes are not pathognomonic of any particular condition, but occur in many nutritional disorders whether these are primary, or secondary to disease of the intestinal tract. Worm infections are included amongst the latter.

In 1943, Krause and Crilly [this *Bulletin*, 1944, v. 41, 139], reporting on 97 cases of *Necator americanus* infection in white adult males, found in varying

degrees " Abnormal function of the mucous membrane manifested by coarsening, irregularity, and obliteration of the folds, and scattering of the barium, and disordered function of the tunica muscularis manifested by abnormally fast or slow transit time, and by hypertonicity with segmentation or by dilatation. . . . They also found that coarsening of the mucosal folds in the mid and distal jejunum was the earliest variation from the normal, and that the mucosal fold was entirely obliterated in a few severe cases. Although barium reached the caecum in one hour or less in many cases, slow transit time and dilatation were seen only in the severe cases. The changes in the jejunum were more marked than those in the ileum."

Of 44 patients who had symptoms, only 4 had normal intestines, and 14 had minimal, 11 moderately severe, and 15 very severe alterations. On re-examination of 29 patients in 5 weeks to 6 months after treatment, 5 of 18 who had had minimal changes later showed normal mucosa, but of 11 with moderate or severe change, none became normal, 8 had improved and 3 showed no change. The authors thus argue that irreversible changes may be produced.

In another series of 125 cases of hookworm infection in United States troops in Assam, HODES and KEEFER (*Amer. J. Roentgenol.*, 1945, v. 54, 728) found " In approximately 60 per cent. of cases roentgenologic abnormalities were demonstrable within one month after exposure to parasites. These abnormalities appeared first in the proximal jejunum and then spread to the distal duodenum and throughout the ileum. Jejunal tenderness was an early sign. In patients with few symptoms the mucosal folds appeared normal but became increasingly thick and distorted with progression of the disease. The jejunal mucosal folds showed striking variations.; the folds appeared thick and irregular, and since their form and direction changed easily and rapidly, they were interpreted as manifestations of an irritable mucosa rather than of organic infiltrations. Active pendulum movements (accordion-like) were often observed, and rarely a " cog-wheel " appearance was recorded which probably reflected a segmental contraction. In seriously ill patients, pronounced abnormalities were common in the third and fourth portions of the duodenum consisting of increased tone as indicated by narrowing of the lumen, irritability and mucosal distortions."

Although improvement occurred when treatment was given, the mucosal folds often remained distorted for weeks after the patient was cured.

The present authors have been on the look out for these radiological changes in the small intestine and have seldom seen the fully-developed changes as reported by Golden. They report three cases of hookworm infection, in one of which there were advanced radiological changes, in one minimal changes, and in one normal findings. In the first cases they report the following changes :—

" A roentgenogram then showed slight widening of some jejunal loops with coarse irregularly mottled or patchy filling (scattering effect) and irregular and ragged mucosal folds. Two or three laterally located loops showed somewhat continuous filling, either moderately narrowed caliber and smooth outline or slightly dilated with coarse serrated outline. The filling of the distal jejunum and proximal ileum was somewhat segmented and blotchy ; the outline of the terminal ileum was quite smooth. The 5-hour examination showed an empty stomach, while distally the barium column had already reached the caecum and ascending colon. The caecum and colon appeared normal. The roentgen impression was abnormal small intestine pattern indicative of some type of disease process which may be brought about by hookworm infection, or by a combination of hookworm infection together with some deficiency process."

L. E. Napier

Floch, H. & de Lajudie, P. Sur le parasitisme intestinal en Guyane française. [**Intestinal Parasites in French Guiana.**] *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 7/8, 265–70.

A further study has been made of the intestinal parasites of French Guiana from 1939 to 1945 inclusive, for comparison with earlier studies by Labernadie and Marneffe [this *Bulletin*, 1930, v. 27, 441].

In a total of 17,179 stools, parasites have been found in 8,885 (51 per cent.) ; there was a parasitism index of 63 per cent. The amoebae were relatively rare but ankylostomes occurred in 33 per cent. of the stools examined, *Trichuris* in 9 per cent., and *Ascaris* in 8 per cent. More than one parasite was found in 10 per cent. of the stools. These figures are lower than those of Labernadie and Marneffe, who found 77 per cent. of positive stools with a parasitism index of 117 per cent., and with the various elements proportionately reduced. The regression of parasitism is also reflected in the marked reduction in poly-parasitism, 32 per cent. of stools compared with 10 per cent.

The authors in their statistics did not separate convicts from the free population for the whole period, but, in two smaller groups, they found 55 per cent. and 61 per cent. positive stools, respectively : on the contrary, of the former only 8 per cent. showed more than one parasite compared with 18 per cent. of the latter. As in the statistics of Labernadie and Marneffe, ancylostomes predominated in the penal group, 75 per cent. of stools compared with 62 per cent. in the free population, but *Trichuris* and *Ascaris* were higher in the free population (13 per cent. and 17 per cent. of stools compared with 9 per cent. and 3 per cent. of stools of convicts).

During 1945, parallel examinations were carried out by the direct method and by Willis's enrichment method. By these two methods the percentages of ankylostome eggs were 73 per cent. and 81 per cent., and *Trichuris* 20 per cent. and 31 per cent., respectively : on the contrary, *Ascaris* eggs were found in 25 per cent. and 15 per cent. of stools by the two methods, respectively. By using both methods, the authors found 72 per cent. positive stools, making an index of parasitism of 99 per cent. Labernadie and Marneffe presumably used only the direct method.

The authors conclude that the rate of parasitism in Cayenne is considerably reduced, especially as regards *Trichuris* and *Ascaris*, since the survey of Labernadie and Marneffe. *L. E. Napier*

Tupas, A. V. & Mañalac-Morales, S. **Intestinal Obstruction Secondary to Ascariasis in Children.** *J. Philippine Med. Ass.* 1948, Jan., v. 24, No. 1, 29–32.

" 1. Seven cases of intestinal obstruction secondary to ascaris were admitted to the Philippine General Hospital within a period of two years.

" 2. All of these cases recovered under conservative management alone, so that surgical intervention was not advocated.

" 3. Stress is laid on an early differentiation between intestinal obstruction due to ascariasis and an acute abdomen requiring surgical intervention."

Woodman, H. M. **Filariasis in the Southern Sudan.** *East African Med. J.* 1948, Feb., v. 25, No. 2, 95–104. [11 refs.]

Wuchereria bancrofti, *Onchocerca volvulus*, *Loa loa* and *Acanthocheilonema perstans* have now been proved to occur in the S.W. Sudan and to extend to the borders of the Belgian Congo and beyond. *L. loa* develops in the common Central African *Chrysops—C. distinctipennis* and *C. longicornis*—but in these

species development is slow and somewhat irregular compared with what takes place in *C. silacea* and *C. dimidiata* in W. Africa.

Three hundred individuals of *C. distinctipennis* and *C. longicornis* were dissected after feeding on *Loa*-infected blood. Growth was slow and 18–20 days were required before the embryo reached the stage of full larval development. Out of 600 caught in the wild state 0·66 per cent. were infected with *L. loa*. Both these species of *Chrysops* were furtive in habits, lacked the voracity of other biting flies, and so were seldom observed to bite man willingly ; they fed mostly on cattle.

This study suggested that some other vector must transmit *L. loa*.

From two surveys of inhabitants living near breeding places of *Simulium damnosum*, in areas where filarial blindness had not been observed it was found that 77 per cent. had *O. volvulus* embryos in the skin.

Antigen was prepared from avian filariae infecting wild doves and gave a positive intradermal reaction in 91 per cent. of cases [but only 24 tests are recorded, of which 2 were negative] harbouring either *L. loa* or *A. perstans*.

P. Manson-Bahr

GIGLIOLI, G. **The Transmission of *Wuchereria bancrofti* by *Anopheles darlingi* in the American Tropics.** *Amer. J. Trop. Med.* 1948, Jan., v. 28, No. 1, 71–85. [13 refs.]

Previous work is reviewed on anopheline mosquitoes of the *Nyssorhynchus* group, and *Aëdes aegypti*, as hosts of *Wuchereria bancrofti*. The present investigations were made in two coastal areas of British Guiana where *Culex fatigans*, *Anopheles darlingi* and *Aëdes aegypti* are habitual house frequenters. In one locality, *Culex fatigans* predominated and in the other *Anopheles darlingi*. For the study of natural infections in wild female mosquitoes, captures were made in the houses at random, and the mosquitoes were brought to the laboratory and dissected the same day. Experimental infections were made with laboratory-bred mosquitoes. The technique was standardized, so that early stage infections of doubtful value were excluded. More than 19,000 mosquitoes were dissected. From the evidence collected in the field and confirmed by experiment, *A. darlingi* is as good as, if not better than, *Culex fatigans* as a vector of *W. bancrofti*. Laboratory experiments proved beyond doubt that the development of *W. bancrofti* proceeds equally well in both species.

As *C. fatigans* does not fly far from its breeding places, this may account for the tendency of filarial infection to spread among the inmates of a single house. The wider flying range of *A. darlingi* presumably favours its visiting many houses, thus distributing the infection over a wider area than *C. fatigans*.

Attempts to infect *Aëdes aegypti* failed entirely. The experiments are fully described and the findings tabulated. *H. S. Leeson*

HARNED, B. K., CUNNINGHAM, R. W., HALLIDAY, Sybella, VESSEY, R. E., YUDA, N. N., CLARK, Mary C., HINE, Carolyn H., COSGROVE, Rachel & SUBBAROW, Y. **Studies on the Chemotherapy of Filariasis. VI. Some Pharmacodynamic Properties of 1-Diethylcarbamyl-4-Methylpiperazine Hydrochloride, Hetrazan.** *J. Lab. & Clin. Med.* 1948, Feb., v. 33, No. 2, 216–35, 8 figs. [14 refs.]

Hetrazan is a new compound which is very promising for the treatment of human filariasis [this *Bulletin*, 1948, v. 45, 353]. It has a low toxicity and few side reactions. For mice, the intraperitoneal LD_{50} (dose causing 50 per cent. mortality) was about 250 mgm. per kgm. and the oral LD_{50} 660 mgm. per kgm.

Single intraperitoneal injections of 100 mgm. per kgm. were readily tolerated by mice, rats, rabbits and dogs. Rabbits tolerated daily intraperitoneal doses of 50 mgm. per kgm. 5 days per week for 14 weeks; rats tolerated a similar schedule of 100 mgm. per kgm., and dogs treated orally tolerated 25 mgm. per kgm. twice daily for 2 months.

The compound was not irritating, produced no local anaesthesia, no effect upon the eye, no effect on the isolated uterus or intestine, and no effect on the blood sugar. It was mildly diuretic and analgesic. Intravenous doses of 2 to 25 mgm. per kgm. in unanaesthetized dogs stimulated the respiration. The heart and blood pressure were not affected by rapid intravenous injections of 0·5 mgm. per kgm., but larger intravenous doses in unanaesthetized dogs produced a transient deviation from the normal. No chemical method for estimation of the drug is known at present; but experimental evidence was obtained that it is rapidly excreted by the kidney, the rate per hour in rats and mice being approximately one-third of the intraperitoneal LD_{50}. *F. Hawking*

Williams, R. W. **Studies on the Life Cycle of** *Litomosoides carinii*, **Filariid Parasite of the Cotton Rat,** *Sigmodon hispidus litoralis*. *J. Parasitology*. 1948, Feb., v. 34, No. 1, 24–43, 8 figs. on 2 pls. [49 refs.]

Antunes, M. L. Notas sôbre a incidência da enterobiose. [**The Incidence of Infestation by** *Enterobius vermicularis*.] *Hospital*. Rio de Janeiro. 1947, Dec., v. 32, No. 6, 971–9, 2 figs. & 1 graph. [12 refs.]

The author examined 100 children attending his clinic in São Paulo, which is connected with the Legião Brasileira da Assistencia, to determine the prevalence of infestation by *Enterobius vermicularis*. The total is, of course, far too small to give a true indication of the prevalence. He chose, as the most reliable method, the NIH swab with Cellophane. The ages of the children ranged from 2 to 10 years. Whereas only one was detected by direct faecal examination, 30 were found at the first swab examination and of 43 examined twice 12 more were detected. Thirty, or less than one in three, of the children had any itching of the anus, and 17 of these were infested and in more than half the positive cases pruritus was not a symptom. As regards age, of 23 between 2 and 3 years 6 were positive, of 31 between 3 and 5 years 14 were positive, of 30 between 5 and 7 years 15, from 7–9 years 5 out of 11, and 3 out of 5 of those up to 10 years of age. Forty-three were boys and 17 of them were positive, of 57 girls 25 were positive, or 42 in all among the 100 examined. The next commonest infestation was by *Ascaris lumbricoides* (36), the third by *Trichuris trichiura* (15). *Giardia intestinalis* cysts were seen in thirty. *H. Harold Scott*

Mac Keith, R. & Watson, J. M. **The Diagnosis and Treatment of Threadworm Infestation.** *Practitioner*. 1948, Apr., v. 160, No. 958, 264–70, 12 figs. [13 refs.]

Deschiens, R. & Lamy, L. La thérapie chimique de l'oxyurose. [**The Chemotherapy of Enterobiasis.**] *Liber Jubilaris J. Rodhain* (*Soc. Belge Méd. Trop., Brussels*). 1947, Dec., 171–94. [13 refs.]

This paper consists of a review of the literature on the chemotherapy of anthelmintic drugs, especially with reference to the treatment of *Enterobius* infection. The drugs considered include santonin, oil of chenopodium, carbon tetrachloride, tetrachlorethylene, bismuth carbonate and subnitrate, the derivatives of triphenylmethane—*e.g.* alkaline fuchsin, gentian violet and

malachite green, and phenothiazine and its derivatives. The authors conclude that drugs of low toxicity which act by causing subacute or chronic poisoning of the worms are preferable.

In enterobiasis, the derivatives of triphenylmethane, the derivatives of phenothiazine, and the carbonate and the subnitrate of bismuth best comply with these requirements. The advantage of phenothiazine compared with the derivatives of triphenylmethane is the greater facility of administration. They can be prescribed in tablet or powder form in the morning on an empty stomach in doses of 0·04 to 0·06 gm. per kilogramme body-weight, in one or two series of 3 to 5 consecutive days, separated by an interval of, say, 3 weeks, whereas the triphenylmethane dyes are given by mouth as glutinous pills, half an hour before meals in two to three series of eight days, separated by 6- to 8-day intervals. If the employment of the latter require qualities of discipline and perseverence in the patient, they at least have a chemotherapeutic coefficient with a generous margin of safety, which is the reason that many writers recommend them as the drugs of choice in enterobiasis, reserving phenothiazine for patients who cannot take the derivatives of triphenylmethane. The authors, however, prefer purified phenothiazine for enterobiasis in healthy adults, but in children and in adults with anaemia or liver and kidney complications, they prefer subnitrate of bismuth. *L. E. Napier*

SKINNER, J. C. **Neurologic Complications of Trichinosis. Report of Two Cases.** *New England J. of Med.* 1948, Mar. 4, v. 238, No. 10, 317–19.

The author briefly discusses the literature on this subject, remarking that, although increasing attention has been given to trichiniasis recently, relatively little has been written about its neurological complications. GOULD (*Trichinosis*, 1945, Thomas, Springfield, Illinois) has reviewed the literature of trichiniasis, and MOST and ABELES, (*Arch. Neurol. & Psychiatr.*, 1937, v. 37, 589) have described three types of microscopic changes seen in the brain at autopsy.

The present author describes two patients, the remarkable features being the disordered mental stages and the neurological signs. The first patient, a woman aged 60, who had eaten a large amount of pork some 4 weeks earlier, had periorbital oedema on both sides, generalized myalgia, fever, nausea and vomiting. She developed increasing apathy and confusion. Orientation in time and space were excellent and there was no aphasia, but there was slight nuchal rigidity. White cells were found in the urine. The white cell count in the blood was 12,250, with 38 per cent. of lymphocytes and 5 per cent. of eosinophiles. Lumbar puncture revealed a yellow cerebrospinal fluid with a pressure equivalent to 110 mm. of water and containing 700 crenated red cells per cmm., with a total protein of " 11 mg. and a sugar of 85 mg. and a chloride of 708 mg. per 100 cc." Three days later, the yellow fluid showed a pressure equivalent to 140 mm. of water, 540 fresh red cells per cmm. and a total protein of 11 mgm. per 100 cc. and a gold-sol curve of 0001111000. The spinal fluid Hinton and Wassermann reactions were negative. An electrocardiogram showed evidence of myocardial disease. Six days after admission, the reflexes in the right arm and leg were slightly more active than those on the left side and two days later the right plantar response was extensor. A " Trichinella-antigen test " on the eighth hospital day was positive and on this day biopsy from the gastrocnemius muscle revealed several *Trichinella* larvae. By this time the mental state had become normal. On the 22nd day there was an eosinophilia of 13 per cent. which continued, with a relative lymphocytosis. The patient rapidly improved and was discharged 5 weeks after admission when she still had an extensor plantar response and increased deep tendon reflexes on the right side.

The second patient was a man, aged 40, who also had periorbital oedema, chills, slight fever, nausea and vomiting. He had diarrhoea and mild muscle pains. Like the first patient he had eaten pork, but the diagnosis of trichiniasis was presumptive only. Physical and neurological examinations were negative, but the blood showed 11,000 to 14,500 white cells with 44 per cent. of eosinophiles, increasing to 64 per cent. during the patient's three weeks in hospital. The urine and cerebro-spinal fluid were normal. Electrocardiograms showed evidence of myocardial damage. On the fourth day the patient showed increasing restlessness, jerky movements and anxiety. He was given paraldehyde, but became noisy and disoriented and needed restraint, delirium tremens being suspected. His condition became critical, but these symptoms lasted only two days, after which he improved steadily, although difficulty in walking developed and on the twentieth day in hospital there was slight left hemiparesis with a left extensor plantar response and a positive Hoffmann reflex in the left hand and slightly more active left knee and ankle jerks. The left leg dragged in walking and sense of position in the left fingers and toes was impaired. Gradual improvement followed and the anxiety disappeared. Five months later he was re-admitted for incipient delirium tremens and then had unsteady gait, with difficulty limited to the left leg; there was an extensor left plantar response.

The author refers to the depressed mentality reported by Most and Abeles (*loc. cit.*) and by SHELDON in their cases [*Bulletin of Hygiene*, 1941, v. 16, 289] and, discussing whether the mental state is due to damage to the central nervous system or is only an effect of severe illness, he considers it reasonable to postulate damage to the brain in some cases. In the cases described above there was, he thinks, evidence of damage to the central nervous system and he discusses other evidence of this kind of damage reported by SPINK (*Arch. Intern. Med.*, 1935, v. 56, 238), Sheldon, (*loc. cit.*), Most and Abeles (*loc. cit.*) and MERRITT and ROSENBAUM [this *Bulletin*, 1937, v. 34, 32]. The first patient recorded above showed three unusual features, namely; (1) the eosinophiles did not reach the high percentage commonly reported and they showed a slow rise in spite of a heavy infestation, this latter feature being regarded by Gould (*loc. cit.*) as a poor prognostic sign; (2) a positive biopsy without muscle tenderness or induration; (3) xanthochromia of the cerebrospinal fluid with 500 to 700 red cells per cmm. on two successive occasions. It seemed that multiple periventricular haemorrhages had occurred. The author remarks that there is need for wider recognition of the protean neurological signs and symptoms of trichiniasis and for further study of them. He thinks it remarkable that epilepsy is seldom a complication of trichiniasis, although DANDY (in *Lewis' Practice of Surgery*, 1945, v. 14, 384, Prior, Hagerstown, Maryland) has reported its occurrence ten years after trichiniasis. *G. Lapage*

DEFICIENCY DISEASES

RUGG-GUNN, M. A. **Nutritional Neuropathy as seen in Ex-Prisoners of War from the Far East with special reference to the Factors responsible for the Distribution of the Lesions in the Central Nervous System.** *J. Roy. Nav. Med. Serv.* 1947, July, v. 33, No. 3, 137–77. [36 refs.]

The author describes the neurological and mental changes attributable to dietary deficiency as they were seen in Japanese prison camps and the results of his own investigations on 53 ex-prisoners.

Nutritional neuropathies are considered in four groups :—

1. Peripheral neuritis, including " electric feet " and cranial nerve lesions.
2. Nutritional amblyopia.
3. Spinal cord involvement.
4. Mental changes.

These manifestations are regarded as parts of a single syndrome, based aetiologically upon a prolonged protein deficiency with a high relative carbohydrate intake and multiple vitamin deficiencies of the B group.

Factors which may be responsible for the distribution of the lesions in the central nervous system are considered in detail and the author concludes that the most important of these factors is phylogenetic seniority, the younger tracts being selected first, the sensory mechanism being relatively more sensitive than its motor counterpart. *Dean A. Smith*

HERNÁNDEZ CAÑERO, A. Beri-beri cardiaco. (Caso clinico). [**A Case of Cardiac Beriberi.**] *Sanidad y Beneficencia Municipal.* Habana, Cuba. 1947, Oct.–Nov.–Dec., v. 7, No. 4, 112–19, 7 figs.

GILLMAN, J. & GILLMAN, T. **Liver Disease in Johannesburg : relation to Pellagra.** *Lancet.* 1948, Jan. 31, 169–73. [16 refs.]

In an earlier paper [this *Bulletin*, 1946, v. 43, 364] the authors have described the pathological findings in biopsy specimens of the liver from Africans with pellagra. The changes were classified under four headings, and further subdivided according to the amount of fat present. The types were :—

i. Fatty infiltration alone.

ii. Cytosiderosis, or accumulation of an iron-containing pigment in hepatic and Kupffer cells.

iii. Cytosiderosis, as in type ii, but with large masses of iron pigment in Kupffer cells and histiocytes of the portal tracts.

iv. Pigment cirrhosis.

The present paper provides a background for these observations. A survey has been made of the histology of the liver in a sample of the general population, represented by an unselected series of 351 people killed by trauma. The same

	General population		Pellagrins
	Africans	Europeans	
Number of cases	261	90	217
Percentage incidence of lesions :			
Type i	2·7	13·3	24·9
,, ii	45·7	36·6	38·7
,, iii	26·4	1·1	26·7
,, iv	9·6	2·2	9·7
Normal	12·6	42·2	—
Other lesions	3·0	4·6	—

classification has been used, and the results of the two investigations may be most conveniently compared in a table, derived from two tables in the authors' text.

These figures show a remarkable correspondence between the pellagrins and the general population of Africans in the incidence of all except the type i lesions. The more chronic changes (types iii and iv) were much less common in Europeans than in Africans. There are two further significant points not brought out by this condensed table: the changes in general were less severe in Europeans than in Africans. Even slight degrees of fatty infiltration or cytosiderosis have been included in the table as type i or type ii lesions. Whether these slight changes should be regarded as pathological is a point upon which the authors do not commit themselves. Secondly, the lesions of all types occurred earlier—by one or two decades—in pellagrins than in the general population of Africans, and earlier in Africans than in Europeans.

The authors have extended their original conception of the way in which these pathological changes are related. "Cirrhosis can supervene at any stage in the course of cytosiderosis, and not only when the liver becomes intensely pigmented". They re-emphasize that cirrhosis is not related to long-standing fatty change. Siderosis, or the appearance of masses of pigment in Kupffer cells and histiocytes, may also develop at any stage in the evolution of cytosiderosis. "Both reactions—namely, cirrhosis and siderosis—represent distinct landmarks in the progress of the disease."

The consequences may extend beyond the liver. It is suggested that the discharge into the circulation of inert pigment of large molecular size may have important effects on other organs, analogous to those produced experimentally by the injection of synthetic polymers, and described by HUEPER (*Arch. Pathology*, 1942, v. 33, 267) under the name "macromolecular syndrome".

Since liver lesions are as common in the general population of Africans as in pellagrins, the question arises of the relationship between pellagra and cytosiderosis. The fact that pigment changes are more extensive and severe in pellagrins suggests that a relation does exist, but this cannot yet be defined with precision. The authors' view may be given in their own words: "In the general population of Africans some types of stimuli are maintaining a perverse intracellular metabolism, having as an end-result the deposition of iron pigment. . . . This perverse metabolism can silently destroy the tissues to such an extent that the patient first becomes severely ill and presents himself at the hospital when he already has an advanced hepatic cytosiderosis, with or without cirrhosis. . . . At any stage during the progress of this pathological process, which to the untrained observer does not express itself clinically, an acute attack of pellagra may be suddenly precipitated." *J. C. Waterlow*

DAVIES, J. N. P. **The Essential Pathology of Kwashiorkor.** *Lancet.* 1948, Feb. 28, 317–20. [25 refs.]

The term kwashiorkor has in recent years been extended by Trowell to include adult as well as infantile cases. Some patients may present in a chronic phase of the disease, with few specific signs except for the presence of undigested food in the stools. This paper describes the histological findings in 50 cases examined at post-mortem or by biopsy; 31 of the patients were less than 10 years old.

In the liver, the histological picture varied with the age. In children under 5 there was always some degree of fatty change. This began in the cells in the peripheral parts of the lobules, and progressed towards the centre, until

eventually every liver cell was loaded with fat. The appearance of fat was accompanied by infiltration of lymphocytes into the portal areas, and proliferation of reticulin fibres into the lobules, surrounding and strangling the peripheral cells. If resolution occurred, the fat disappeared first from the centro-lobular regions, and last from the periphery. Great stress is laid on the predominantly peripheral distribution of the fat: if fat is mid-zonal, central, or irregular " some serious complication is to be suspected, and the condition is probably secondary kwashiorkor ". The disappearance of fat may or may not be accompanied by clinical improvement. When all fat has disappeared, the liver is left with a patchy monolobular cirrhosis, with collections of lymphocytes at the edges of the lobules. This picture is the " hallmark of kwashiorkor ", and persists throughout life. It has been found in almost every case in a series of more than 1,000 post-mortems.

In older children and adults, fatty change was absent or slight, except in a group of adult immigrants from the Belgian Congo. All cases presented the typical clinical picture of kwashiorkor, regardless of whether the liver was fatty. Therefore the fatty change, so prominent in infants, cannot be looked upon as the essential lesion in this disease. With increasing age the fibrosis became more severe; the final picture was a pure monolobular cirrhosis, similar to that described by VINT [this *Bulletin*, 1931, v. 28, 842]. In most cases this seemed to be complicated in the later stages by focal necroses, with regenerative hyperplasia and replacement fibrosis, producing a mixed type of cirrhosis. In contrast to the findings in Johannesburg, there was no excess of iron pigment, and the condition never progressed to haemochromatosis. Malaria and helminthiasis were present in a few cases, but there was no evidence that these were related to the liver lesions.

Changes were also found in the kidney and pancreas. The kidneys showed hyalinization of the glomeruli, with metaplasia of the capsular epithelium and pericapsular fibrosis.

In the pancreas, the earliest change was atrophy of the acinar cells, followed by hyalinization and fibrosis. In late cases the acini had disappeared over wide areas of the pancreas. Cyst formation and metaplasia of the ductal epithelium were not found; the condition therefore differs from cystic fibrosis of the pancreas described by ANDERSEN (*Amer. J. Dis. Children*, 1938, v. 56, 344). There was an indication that in the early stages the islets were hyperplastic; later some seemed to disappear.

Attention was first directed to the pancreas because some patients admitted as diabetics in hyperglycaemic coma, when treated with insulin, passed into hypoglycaemic coma, which did not respond to treatment with glucose. At post-mortem, the pancreas in such cases was found to be almost completely fibrosed. It was then discovered that fibrosis of the pancreas was extremely common. It was found in two-thirds of 165 routine autopsies, and in every one of 13 cases of kwashiorkor. It is therefore suggested that pancreatic fibrosis is a kwashiorkor lesion, and that the disease is initially a result of pancreatic deficiency, itself caused by malnutrition. This view is supported by the constant finding of undigested and unabsorbed food in the stools. It could also explain the common but not invariable association of kwashiorkor with fatty infiltration of the liver, since fatty liver has been produced in dogs by extirpation of the pancreas.

If this assumption is correct, treatment should logically be directed to restoring pancreatic function. In this connexion the interesting observation has been made that one of the first signs of clinical improvement was swelling of the salivary glands, which are closely related morphologically to the pancreas.

J. C. Waterlow

MAGALHÃES CARVALHO, PINTO, A. G., SCHMIDT, M. M., POTSCH, N. & COSTA, N. Distrofia pluricarencial hidropigência. [**Dystrophy with Oedema and Signs of Multiple Nutritional Deficiency.**] *J. Pediatria.* Rio de Janeiro. 1945, Nov.–Dec., v. 11, Nos. 11/12, 395–439, 7 graphs & 7 figs. [83 refs.)

——. A esteatose hepática na distrofia pluricarencial hidropigênica da infância. [**Fatty Liver in Infants with Dystrophy, Oedema and Multiple Nutritional Deficiency.**] *Medicina, Cirurg., Farmacia.* 1946, June, No. 122, 1–16. [17 refs.]

DE MAGALHÃES CARVALHO, J. Contribuição ao tratamento da distrofia pluricarencial hidropigênica. [**A Contribution to the Treatment of Dystrophy with Oedema and Multiple Nutritional Deficiency.**] *Hospital.* Rio de Janeiro. 1947, Sept., v. 32, No. 3, 307–26, 6 figs. [28 refs.]

Oedema was the criterion used in selecting the cases described in these three papers. The syndrome as a whole, however, appears to be identical with kwashiorkor in Africa. [The word is here used in its original sense (see WILLIAMS, this *Bulletin*, 1934, v. 31, 344) and not with the wider meaning recently attached to it by TROWELL (*ibid.*, 1945, v. 42, 306)]. The age incidence ranged from 4 months to nearly 6 years. Of 58 cases, 14 were white, 32 mixed, and 12 black. [The racial incidence is of interest because kwashiorkor has seldom been described in white children. It has been suggested that the disease is confined to peoples of African stock—a theory that can no longer be upheld in view of the present results from Brazil, the observations of HANAFY (this *Bulletin*, 1948, v. 45, 458) in Egypt, and earlier reports from Central America.]

The history was of a diet consisting almost entirely of carbohydrate. Diarrhoea was common. In many cases the presenting sign was oedema. This was of the dependent type, sometimes generalized and very severe. The skin was dry and inelastic, with branny desquamation. In most cases there was an extensive, diffuse hyperpigmentation, described as "Addisonian". Thirty-eight cases showed other skin lesions as well; most commonly there were irregular hyperpigmented patches, with sharply defined edges, and a more or less symmetrical distribution. The sites of election were the thighs, perineum, and gluteal region. The lesions began as discrete papules round hair-follicles; these became pigmented and coalesced; the pigmentation deepened, and the superficial layers desquamated, leaving a delicate pink skin underneath. Biopsy of the skin showed atrophy of the basal and Malpighian layers, with oedema and degenerative changes in the corium. These findings are illustrated in the first paper by photomicrographs. The lesions were more common in the black children than in the white or mixed. In other cases there were smaller hyperpigmented areas, which appeared without initial erythema.

The hair was, in general, dry and depigmented, and the scalp covered with seborrhoeic crusts. In a few cases there was xerophthalmia. Angular stomatitis was common; the tongue usually showed atrophy of the papillae, although in some cases there was a frank glossitis. Examination of the heart showed tachycardia with marked sinus arrhythmia. Occasionally inversion of the T-wave was found in the electrocardiogram. Tendon reflexes were diminished or absent in more than half the cases, and the calves were tender to pressure. The liver was usually enlarged, with a smooth regular edge, but the spleen was not palpable. At post-mortem, gross fatty infiltration of the liver was a constant finding. This was not related to the degree of enlargement. Other autopsy findings are not recorded. Evidence of osteoporosis was observed in X-ray examinations.

Laboratory examinations were mainly of negative interest. Helminthiasis was found in only a quarter of the cases. There was a variable degree of anaemia, sometimes with a mild macrocytosis. Estimations on serum showed reductions

in the mean values for calcium (7·39 mgm. per cent.), phosphorus (3·36 mgm. per cent.), cholesterol (88·5 mgm. per cent.) and phospholipids (6·1 mgm. per cent.). The total protein and albumin concentrations were very low, but the globulin content was normal (means: 4·13, 1·97 and 2·17 gm. per cent. respectively). The relation of these findings to oedema is discussed at length in the first paper. Although in most cases total protein and albumin concentrations were below the so-called oedema level, this was not always so. Moreover, in cases responding to treatment it was sometimes found that, as oedema disappeared, the total protein and albumin concentrations did not rise, but were even further reduced. It is suggested that the serum proteins may be not only reduced in quantity, but also qualitatively altered in such a way that they do not exert their normal osmotic pressure, and that under treatment the normal composition is restored before the amount.

Analysis of these findings showed that the condition was one of multiple deficiency, involving protein, minerals, vitamin A, thiamin, riboflavin, nicotinic acid and probably other members of the vitamin B_2 complex. However, at an early stage it was found that, in spite of the presence of signs of specific deficiency, treatment with the vitamins concerned not only failed to cure, but actually made the disease worse. Moreover, none of the signs noted seemed to be in any way related to the severity of the general condition, or to be of any value in assessing the prognosis. For these two reasons, from the end of 1944 onwards, attention was focussed on the fatty liver, which was felt to be the central feature of the disease.

The harmful effect of vitamins was explained by the experimental findings of HANDLER, MCHENRY, and others, that in rats choline-deficiency does not produce a fatty liver if B-vitamins are absent from the diet. Under the conditions of their experiments, when vitamins were given, the amount of fat in the liver increased. Moreover, since diets low in the B-complex are likely also to be low in choline, it was logical to suppose that the fatty liver in these infants was the result of choline deficiency. This theory was tested by giving choline in various doses, and measuring the serum phospholipid content after an interval of 6–48 hours. It was thought that, on current theories of the lipotropic action of choline, there should be an increase; no such increase was found, nor did there seem to be any beneficial effect on the general condition.

On the theory of choline-deficiency it was difficult to explain the presence of fatty liver in these infants in spite of an inadequate intake of B-vitamins, as shown by the clinical signs of avitaminosis. Magalhães Carvalho and his colleagues, therefore, turned their attention to types of fatty liver that are not caused by choline-deficiency, such as that produced in dogs by excision of the pancreas, and cured by the pancreatic extract "lipocaic". Fifteen cases were treated with lipocaic, with apparent success. The authors are, however, careful to point out that the results were not significantly better than with milk alone, and that the main point in treatment is to avoid giving vitamins. The results in detail were as follows:—

Dried skimmed milk with vitamins, liver extract, and plasma, etc.	35 cases, 10 deaths
Dried skimmed milk alone	8 cases, 1 death
Dried skimmed milk with lipocaic	15 cases, no deaths

The rôle of the pancreas was further emphasized by the finding that in convalescent cases there was a reduced secretion of pancreatic lipase and trypsin. These observations are briefly mentioned, and not reported in full. The conclusion is drawn that in this syndrome the primary and essential lesion may be of the pancreas and not of the liver.

Comment

[The discovery of anatomical and functional lesions of the pancreas in kwashiorkor marks a new and important stage in our knowledge of the disease. It is remarkable that the same conclusion should have been reached independently and more or less simultaneously in three different parts of the world. In addition to the work of DAVIES and of MAGALHÃES CARVALHO, Professor VÉGHELYI has recently (*Lancet*, 1948, Mar. 27, 497) reported from Budapest that when infants were deprived of milk during the siege, there was a decrease of pancreatic secretion which preceded the development of nutritional oedema and fatty liver. Such observations form a logical sequel to the earlier work of Scott BROWN and TROWELL [this *Bulletin*, 1945, v. 42, 306] on the deficiency bowel pattern.

Atrophic changes in the pancreatic acinar cells were observed in infants with fatty liver in the West Indies [WATERLOW, this *Bulletin*, 1947, v. 44, 841] but no conclusions were drawn about the relationship between the two lesions. Magalhães Carvalho implies, and Davies explicitly suggests, that fatty liver may be secondary to pancreatic damage, on the analogy of the fatty liver produced in dogs by pancreatectomy. This fits in with the fact that the disease does not respond to treatment with methionine [GILLMAN and GILLMAN, *ibid.*, 1945, v. 42, 748] or choline [MAGALHÃES CARVALHO, above; WATERLOW, *ibid.*, 1947, v. 44, 841; *Med. Res. Council Spec. Rep. Ser. No. 263*, 1948], whereas most workers have obtained good results with milk alone (Véghelyi, Magalhães Carvalho, Waterlow). The final link in the chain may be provided by the observations of FRIEDMANN and FRIEDMANN (*Canadian Med. Ass. J.*, 1946, v. 55, 15) who produced atrophic changes in the pancreas and fatty liver in rats on a diet low in protein.

If, as Davies suggests, kwashiorkor is essentially a pancreatic disorder, it would resolve a puzzling paradox: TROWELL [this *Bulletin*, 1941, v. 38, 722; 1945, v. 42, 306] has convincingly described the disease as a multiple deficiency state, involving almost all known factors. For this reason its limits have been extremely hard to define. At the same time, all observers have clearly felt that it *is* a definite disease, and this feeling has inspired a constant search for an essential lesion. The apparent contradiction would be removed if the essential lesion were one involving the splitting, absorption, and intestinal synthesis of nutrients.

It has become increasingly clear from the careful work over many years of Trowell, the Gillmans, and their collaborators, that kwashiorkor cannot be looked upon as an isolated episode of infancy or early childhood. Its consequences extend throughout life, since it may cause irreversible changes such as fibrosis of the pancreas and liver, and other lesions of which we know little. Moreover, even in adult life, the causes of kwashiorkor are never far away. The diet remains insufficient and unbalanced, so that the resulting picture is often very complex—of acute episodes superimposed, in the Gillmans' phraseology, on the chronic effects of a perverted metabolism.

Thus, even if it is established that the initial lesion is in the pancreas, there is much that remains to be discovered about the natural history of the disease and the relationship of its various features. In particular, great interest attaches at the present time to the pathological changes found in the liver, both in children and adults. It may therefore be of interest to examine in greater detail some of the observations in the papers summarized above.

In their earlier work Gillman and Gillman implied the existence of a close relationship between cytosiderosis of the liver and pellagra. This position led to difficulties: in the first place, cytosiderosis does not appear to have been found in pellagrins elsewhere; secondly, it tended to narrow the field of enquiry

into the cause of the liver lesion. It is clear, however, from their present paper and that of Davies that liver lesions in Africans are almost universal; their distribution, in fact, is wider than that of pellagra, malignant malnutrition, or kwashiorkor in its infantile form [this *Bulletin*, 1934, v. 31, 344]. Cytosiderosis cannot be regarded as a hallmark of pellagra, since it is equally common in non-pellagrins. It may, therefore, seem illogical to look upon monolobular fibrosis as the hallmark of kwashiorkor. This difficulty is avoided by the statement of Trowell, that every African passes through a kwashiorkor phase, manifested by pot-belly and failure of growth. The connexion between this malnutritional phase and the ever-present fibrosis cannot, however, be regarded as proven. This caution is dictated by the fact that, whereas cirrhosis is admittedly common in malnourished peoples, this particular type of monolobular fibrosis seems not to have been described outside Africa.

In the case of fatty liver, Davies has shown that this cannot be "a kwashiorkor lesion", since cases may present all the clinical signs of that disease with no fat in the liver. The complement of this has been found in the West Indies [Waterlow, *loc. cit.*]. Infants may show gross fatty infiltration of the liver, and die apparently from hepatic failure, with oedema but none of the other manifestations of kwashiorkor. There was also evidence, obtained by biopsy, that milder degrees of fatty change were quite common in infants apparently healthy, except for slight weight loss. Therefore it would seem that in babies fatty liver may be looked upon as a distinct entity, an effect of malnutrition separable from other signs of deficiency. It is in no way specific to kwashiorkor, but may also be found in malnourished infants in Europe, as in cases of *mehlnährschaden* (Waterlow, 1947; Véghelyi, 1948).

The conclusion, then, must be that liver lesions of various types (fatty change, cytosiderosis, cirrhosis) are widespread among the malnourished populations of the tropics, but it is not yet possible to relate any particular lesion to a specific clinical picture.

When the papers of Davies and the Gillmans are considered together, the question arises: why should iron pigmentation be found in one group and not in the other? No answer is yet possible. Cytosiderosis, as far as present information goes, seems to be peculiar to the Rand, whereas cirrhosis in one form or another is common throughout the tropics. An important observation, which may be relevant, has been made by Gillman and Gillman (1945). In refuting the view that cytosiderosis might be caused by anaemia, they pointed out that their patients were not anaemic, and did not suffer from malaria or ankylostomiasis. All these conditions are endemic in East Africa, and in most parts of the tropics. It is therefore possible that, other things being equal, the absence of cytosiderosis is related to the presence of diseases which increase the body's demand for, and turnover of, iron.

The end-results of fibrosis in the liver tend to be much the same, whatever the initial cause. Therefore conclusions derived from experimental cirrhosis in animals cannot easily be applied to man until more is known about the development and early stages of the human disease. Davies's observations are here of particular value, and go far to fill the gap, although none of the types of dietary cirrhosis produced in animals corresponds exactly to monolobular cirrhosis in man. It is not clear whether the workers in East Africa believe that fibrosis is in any way caused by fatty infiltration. In the West Indies the same picture was found, of reticulum fibres growing into the edge of the liver lobule (Waterlow, *loc. cit.*). From the scanty evidence available, it seemed that the end-result was a fibrosis of the Laennec type, similar to that produced in dogs with fatty liver by Chaikoff and his co-workers (*Amer. J. Path.*, 1943, v. 19, 9)

This brief summary draws attention to three questions in relation to the liver lesions:—

1. Is fibrosis caused by preceding fatty infiltration ?
2. Is fibrosis of the liver, as found in under-nourished peoples, a pathological entity, or does it have different modes of development under different circumstances in different parts of the world ?
3. What is the relationship of iron pigmentation to the other changes ?

It is clear that these questions can only be fully answered in the light of information from all parts of the world where malnutrition exists. In recent years the study of the more acute forms of the disease has gone forward with great speed in many different countries, and this gives great promise for the future.] *J. C. Waterlow*

HAEMATOLOGY

GOSDEN, Minnie & REID, J. D. **An Account of Blood Count Results in Sierra Leone.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 637–40.

This paper analyses the results of 1,035 total red cell and 1,005 white cell counts done on adult Africans at the Government Laboratory, Freetown, between 1943–1946.

The chief object of the survey was to compare adult African blood standards with European " normals " and to determine the locally prevailing types of anaemia. The samples were those for routine examinations for anaemia or from patients who felt " run-down ". The patients came from all social grades, but classification on a social basis was not possible : in view of varying dietetic standards, such a classification would have been a factor of importance.

Many of the anaemias did not respond to either iron or liver therapy alone, and required a combination of both : they probably corresponded with Trowell's dimorphic type [this *Bulletin*, 1943, v. 40, 938].

Standard methods of examination were employed and are described and the European standards adopted for comparison were those given by WHITBY and BRITTON (*Disorders of the Blood*, 1942, 4th Edition. London : Churchill).

The results are shown in four tables. These show that 26 per cent. of 661 men had red cell counts of at least 5 million cells per cmm. and 72 per cent. were at least 4 million : about two-thirds of the latter had normal values for mean corpuscular haemoglobin and mean corpuscular volume. Of 377 women, 56 per cent. had red cell counts of at least 4 million cells per cmm., and of these over half had normal M.C.H. and M.C.V. values.

In 109 moderate anaemias in men, 57 per cent. were orthochromic normocytic and of the 74 more severe anaemias, 40 per cent. were orthochromic and 39 per cent. were normocytic. Hypochromic microcytic anaemia was about twice as common as macrocytic hyperchromic anaemia.

In 99 moderate anaemias in women, about half were orthochromic normocytic and this form was also seen in 64 severe anaemias. The microcytic hypochromic type was about 3 times as common as the macrocytic hyperchromic type.

The sickle-cell trait was found in 27 per cent. of all the bloods examined.

Of the white cell counts in 646 men and 359 women, 79 per cent. were within normal limits and 5 per cent. showed leucopenia ; eosinophilia occurred in 40 per cent. of men and 17 per cent. of women and a monocytic increase was present in 34 per cent. of men and 42 per cent. of women.

During the same period, 7 cases of myeloid and 1 of lymphatic leukaemia were seen.

The authors conclude that in adult Africans in the Freetown area blood cell counts and haemoglobin levels appear to be within the accepted normal levels

for Europeans: that an orthochromic normocytic anaemia is the commonest type: that microcytic hypochromic is commoner than macrocytic hyperchromic; and that about one adult in four has the sickle-cell trait.

[It is now almost a platitude to observe that efforts to arrive at haematological and other "normals" in Africans are of prime importance; and until acceptable physiological standards are arrived at, many forms of pathological research must remain without an adequate foundation. Surveys of the kind described above are greatly to be commended; but the difficulty still remains of assessing "the normal" African in the first instance; for example, in the above series, all the persons examined were patients complaining of some degree of ill-health. The present reviewer, in a small study of the polynuclear count in East Africans many years ago (this *Bulletin*, 1931, v. 28, 837), set out to obtain a control series of healthy Africans who would be sufficiently free of any disease—and particularly any infection—which might be likely to influence their haematological state. Experience showed what immense difficulties existed: anything which clarifies the physiology of Africans in their present background increases the possibilities of understanding, and therefore of rectifying, their pathological status. See also HENNESSEY, this *Bulletin*, 1937, v. 34, 256.]

H. J. O'D. Burke-Gaffney

BOTURÃO, Edg. & BOTURÃO, Edm. Doença por hematias foiciformes (Sickle-Cell Disease). Incidência na Santa Casa de Santos—observações clínicas e haematológicas. [**Observations on Cases of Sicklaemia in Santa Casa Hospital (Rio de Janeiro).**] *Hospital.* Rio de Janeiro. 1947, Nov., v. 32, No. 5, 709–28, 4 figs. [38 refs.] English summary.

Three cases of this condition are described from among 20 detected in examining 294 coloured persons; 64 white persons were examined, but none of these was affected. Of the 294 there were 162 negroes and 132 mulattoes and those with sicklaemia numbered 14 and 6 respectively. The histories of the three were very different. One (No. 3 in the cases detailed) had fever, cough, and pain in the chest and was diagnosed as suffering from lobar pneumonia; a second (No. 2) had fever, palpitation, dyspnoea, tinnitus, and prostration from weakness. The third (No. 1) in the midst of enjoying excellent health suddenly complained of "feeling very ill" and lost consciousness; he was brought to hospital in a comatose condition which persisted for 3 days and was followed by transient aphasia and dysarthria, so that no proper account could be obtained for 10 days and even then there was some degree of mental confusion, but he remembered telling his fellow-worker that he was feeling ill. Wassermann reaction was negative with both serum and cerebrospinal fluid. The blood changes are described fully and were those usually seen in this disease; the sedimentation rate was much reduced, ranging between 3 and 15 mm. in the first hour. The erythrocyte count also varied widely. In No. 1 it was 3,480,000 and Hb 80 per cent., and 7 weeks later 4,240,000, with Hb 85 per cent.; in No. 2, the first count gave only 800,000 per cmm. and Hb 30 per cent.; 3 weeks later 2,000,000 and Hb 62 per cent.; after another week he had another febrile attack and the red cells fell to 620,000 and Hb to 18 per cent., increasing in a fortnight to 1,740,000 and Hb 45 per cent. After this he improved slowly, but at times complained of headache and giddiness and had, occasionally, bouts of fever to 40°C. No. 3 was not so ill; his counts ranged during the first ten days' observation about 2–2½ million per cmm. and Hb 62–70 per cent. and in another ten days the figures were 3,120,000 and 70 per cent. The residual red corpuscles in 0·2 per cent. saline in this patient became elliptical and remained so for 24 hours. These are regarded by the author as "regression forms of '*in vivo*' sickled erythrocytes possessing greater resistance."

H. Harold Scott

Farreras Valentí, P. Fisiopatologia y clinica de las anemias carenciales. (Con exclusión de las ferropénicas y perniciosa genuina). [**Physiopathological and Clinical Aspects of Nutritional Anaemias, other than Iron Deficiencies and Pernicious Anaemia.**] *Semana Méd.* 1948, Mar. 4, v. 55, No. 10, 383–99, 1 fig. [39 refs.]

VENOMS AND ANTIVENENES

Macchiavello, A. **Cutaneous Arachnoidism experimentally produced with the Glandular Poison of** *Loxosceles laeta*. *Puerto Rico J. Pub. Health & Trop. Med.* 1947, Dec., v. 23, No. 2, 266–79, 3 figs. [Spanish version 280–93.]

Study has been undertaken of the poison or poisons of the spider *Loxosceles laeta* which occurs in Antofagasta, Chile. The lesion produced in man is known as "gangrenous spot." The spider abounds in damp, dark and dirty places, and many were captured in mud and straw huts. Experiments were made with rabbits, rats and white mice at first, but later guineapigs were used solely. The lesions varied in severity from oedema without induration to oedema with induration and to gangrenous spot followed by necrosis and ulceration. In man the same sequence of events occurs, but without general systemic disturbance. The severity differs from one spider to another, and whether the bite (or sting) is the first or not, and whether the insect has been kept caged and fasting. Stings of the black or greyish-black specimens are the worst; they are usually the young ones. The more concentrated the poison (that is, glandular matter ground up and emulsified in saline) the less intense the reaction; this is ascribed to the fact that the concentrated poison causes mass coagulation of the tissues and this impedes diffusion. The glandular poison seems to act only on or in the skin; it is not haemolytic. The arachnolysin extracted from the cephalothorax or abdomen differs in its action from the glandular poison from the stingers and there is no cross-immunity between them. Moreover, the arachnolysin is strongly haemolytic for guineapig erythrocytes and still more for rabbit corpuscles and is not necrotizing.

H. Harold Scott

Ramirez L., R. Obtención de veneno de alacrán por estimulación eléctrica. [**The Extraction of Venom from Scorpions by Electrical Stimulation.**] *An. Escuela Nac. Ciencias Biol.* Mexico. 1947, Aug. 15, v. 4, No. 4, 383–5, 4 figs. English summary (5 lines).

Ramirez L., R. Datos preliminares fisicos y quimicos del veneno de alacrán. [**Preliminary Data on the Physical and Chemical Characters of Scorpion Poisoning.**] *An. Escuela Nac. Ciencias Biol.* Mexico. 1947, Aug. 15, v. 4, No. 4, 379–82. [11 refs.] English summary.

DERMATOLOGY AND FUNGUS DISEASES

León Blanco, F. & de Laosa, O. **The Primary Lesion of Pinta. (Mal del Pinto or Carate).** *Amer. J. Syph.* 1947, Nov., v. 31, No. 6, 600–609, 9 figs.

There are three stages in the clinical course of pinta, the initial lesion, secondary widespread skin lesions or pintides and the tertiary dyschromic stage. The present study was presumably carried out in Cuba.

Five to ten days, or earlier, after infection a small papule develops. By the 20th to 26th day, it is larger, flat and slightly desquamating. By the 30th–50th day, the lesion is a flat reddened scaly patch. Satellite papules may develop and later coalesce with the enlarging initial lesion. The final appearance may resemble psoriasis, trichophytosis, lichen or may be that of large pink desquamating patches with infiltrated edges which are often separated by atrophic skin.

In the early papular stage, itching is constant but it is less marked later. The intial lesion is usually on an exposed part of the body, especially the leg and dorsum of the foot (63 per cent. of 257 cases) and the forearm and dorsum of the hand (22 per cent.).

The disease is usually acquired during the first two decades of life, but begins after the first year or so.

The lymphatic glands, in the primary and secondary stages, are enlarged, painless and movable.

The incubation period in experimental infections is 3–10 days, but longer periods, up to 60 days, have been reported.

In 39 naturally acquired infections of 40 days' to two years' duration, the "serologic flocculation and complement fixation tests were negative". In 17 experimental infections, the reactions became positive after the appearance of pintides.

The histopathological changes in the initial lesion include acanthosis with increased length of narrow rete processes, active infiltration by lymphocytes and polymorphonuclear cells and the development of oedema. In the cutis there is perivascular infiltration by lymphocytes and plasma cells. Treponemata are numerous, particularly in the epidermis. [The illustrations of initial lesions are excellent.] [See also this *Bulletin*, 1945, v. 42, 584.]

C. J. Hackett

ALLEN, A. C. **Persistent "Insect Bites" (Dermal Eosinophilic Granulomas) simulating Lymphoblastomas, Histiocytoses, and Squamous Cell Carcinomas.** *Amer. J. Path.* 1948, Mar., v. 24, No. 2, 367–87, 24 figs. on 6 pls. [11 refs.]

This article describes the histology of the cutaneous reactions to "bites" of ticks, chiggers, mosquitoes and unidentified arthropods. The author emphasizes that these reactions may last as long as two years and may exhibit a very variable microscopical picture. The cellular reaction in the dermis, characterized by large numbers of eosinophilic leucocytes, plasma cells, and histiocytes, may be mistaken for Hodgkin's disease, mycosis fungoides, atypical lymphoblastoma, histiocytoses, or the eosinophilic granular group. An appearance closely simulating that of squamous-cell epithelioma may be produced by a section which cuts obliquely through the hyperblastic epidermis and its branching rete pegs. No difference was noted in the histological reaction to "bites" of the various arthropods except for the almost complete absence of eosinophilic leucocytes in the eschar of scrub typhus caused by the larval mite (*Trombicula akamushi* and related species). *H. T. H. Wilson*

JOLLY, H. R. **Prevention of Ringworm in the Tropics.** *Brit. Med. J.* 1948, Apr. 17, 726–8, 1 graph.

This article describes an experiment in the control of ringworm in the Netherlands East Indies, where the disease had reached epidemic proportions and very severe cases were not uncommon. Four hundred British troops were selected for the experiment, which aimed at the prevention of spread of infection from the feet of one soldier to those of another

Two pairs of underpants were issued to each man, and these were washed and changed daily. Each man was given two foot-towels, which were used on the feet only, and were washed and changed daily. Clogs were provided to be worn in the bathroom, where showers were used and not baths. This enabled the toes to be washed without removal of the clogs, and consequently the feet were never brought into contact with the bathroom floor. The men were not allowed to walk bare-footed around the buildings.

Infected cases were not segregated, and the following routine treatment was used with occasional modifications :—

Lesions on the body.—One per cent. chrysarobin in Lassar's paste.
Lesions on the face.—Whitfield's ointment.
Lesions between the toes.—Brilliant green 1 in 500 in spirit with 3 per cent. salicylic acid.

By these means, the number of new cases of ringworm was reduced from 91 in May 1946 to 13 three months later, and this result was achieved without interference with the normal working routine. *H. T. H. Wilson*

Howell, A., Jr. **The Efficiency of Methods for the Isolation of *Histoplasma capsulatum*.** *Pub. Health Rep.* Wash. 1948, Feb. 6, v. 63, No. 6, 173–8, 3 figs. on 2 pls. [11 refs.]

From the spleens of 79 guineapigs experimentally infected with a single strain of *Histoplasma capsulatum*, sowings were made in duplicate on two different culture media; brain-heart-blood-agar and potato-dextrose-agar with penicillin and streptomycin added. One set of cultures was incubated at 37°C. and the other at room temperature.

Of the cultures incubated at room temperature, 35 out of 46 (76·1 per cent.) on brain-heart-blood-agar and 19 out of 46 (41·3 per cent.) on potato-dextrose-agar were successful, while those incubated at 37°C. yielded only 6 successful growths out of 46 sowings on brain-heart-blood-agar and none on potato-dextrose-agar. These results would indicate that brain-heart-blood-agar is a more suitable medium than potato-dextrose-agar and incubation at room temperature much better than at 37°C. [It should be noticed, however, that only a single strain of *H. capsulatum* was used, and strains of this species vary in their adaptability to saprophytic vegetation at 37°C.] [Only the mycelial form of the fungus is mentioned in the paper and it is well known that the optimal temperature for vegetation in this form is far below 37°C.; in fact some strains cannot vegetate in the mycelial form at this temperature. On the other hand, 37°C. is the optimal temperature for vegetation in the yeast-like form and, on blood-agar, at this temperature yeast-like primary cultures frequently develop. Subject to this qualification, the author's findings are in harmony with the general experience of mycologists.] *J. T. Duncan*

Cross, F. W. & Howell, A., Jr. **Studies of Fungus Antigens. II. Preliminary Report on the Isolation of an Immunologically Active Polysaccharide from Histoplasmin.** *Pub. Health Rep.* Wash. 1948, Feb. 6, v. 63, No. 6, 179–83.

The polysaccharide fraction was isolated from crude histoplasmin by precipitation with ethyl alcohol (4 vols. of 95 per cent.), after previous removal of the protein fractions. The yield of dry polysaccharide was approximately 0·34 mgm. per ml. of the crude solution. Tests of dermal sensitivity made on a group of guineapigs experimentally infected with *Histoplasma capsulatum*, and a number of normal control animals, showed the polysaccharide to be an effective reagent. Compared with the stock, crude histoplasmin, and desiccated

crude material, the polysaccharide at a dose of 0·1 mgm. in 0·1 ml. gave a positive reaction in 93·9 per cent. of the guineapigs sensitized with *H. capsulatum*; histoplasmin, at a dose of 0·1 ml. of 1 : 100 solution, in 85·3 per cent. and desiccated histoplasmin at a dose of 0·1 mgm. in 0·1 ml. in 81·8 per cent. Lower proportions of reactors and smaller reactions were given by all three reagents when they were used in lower dosage, but even at the dose of 0·001 mgm. per ml. the polysaccharide gave positive results in 45·5 per cent. of the animals.

As the polysaccharide fraction represents only about 1 per cent. of the total solids of histoplasmin, it seems that there are other antigenic fractions in the crude material.

To test for cross reactions, guineapigs infected with *Blastomyces dermatitidis*, which were highly sensitive to blastomycin, were used with the histoplasmin polysaccharide. The proportions of positive reactors at the various doses were as follows: 0·1 mgm. 48·1 per cent., 0·01 mgm. 25·9 per cent. and 0·001 mgm. 3·7 per cent. The comparable proportions with *Histoplasma* inoculated animals were: 93·9 per cent., 78·8 per cent. and 45·5 per cent.

J. T. Duncan

TENENBERG, D. J.; HOWELL, A., Jr.; FURCOLOW, M. L.; BUNNELL, I. L. **A Complement Fixation Test for Histoplasmosis. I. Technic and Preliminary Results on Animal Sera** [TENENBERG & HOWELL]. *Pub. Health Rep.* Wash. 1948, Feb. 6, v. 63, No. 6, 163–8. **II. Preliminary Results with Human Sera** [FURCOLOW, BUNNELL & TENENBERG]. *Ibid.* 169–73.

The significance of dermal sensitivity to histoplasmin, in the absence of clinical and mycological evidence of active histoplasmosis, remains undetermined. It is imperative therefore that the diagnostic value of serological tests in this disease should be explored.

I. The first paper deals with the complement-fixation test applied to the serum of experimentally infected guineapigs. The antigen used was the 1 : 100 dilution of the histoplasmin skin test reagent (H.15) and the technique was based on Kolmer's modification of the Wassermann test. Of the sera from infected guineapigs, 5 out of 12 gave complete fixation of complement, while sera from 33 uninfected guineapigs all gave negative results. Cross reactions between *Histoplasma* antiserum and *Blastomyces* antigen (the 1 : 100 blastomycin skin test reagent) and between *Blastomyces* antiserum and *Histoplasma* antigen occurred, but by preparing serial dilutions of the serum a point could be reached at which complement-fixation was given only with the homologous antigen. These cross reactions when relatively low dilutions of the sera are used are in harmony with the cross reactions described by HOWELL [*Bulletin of Hygiene*, 1947, v. 22, 569] in connexion with the histoplasmin and blastomycin skin sensitivity tests. Dilution of the crude antigens beyond the stock 1 : 100 strength greatly weakened the reaction, and it is suggested that a much stronger antigen or a purified preparation should be used. It is also suggested that the immune bodies on which dermal sensitivity and the complement-fixation tests depend may not be identical, and the complement-fixation test should provide better diagnostic evidence of existing infection.

II. The second paper deals with the application of the complement-fixation test to human sera, following the technique used in the tests on guineapig sera. Complete complement-fixation was given with 6 out of 9 sera from proved cases of histoplasmosis; 2 out of 13 sera of persons (chiefly children) who, after an earlier negative skin test result, were found to have developed dermal sensitivity to histoplasmin, which suggests recent infection; and 6 out of 36 sera of persons, with active pulmonary lesions, who were histoplasmin-positive and tuberculin-negative. Allowance should be made for the probability that

some of the sera had been collected after the specific antibody titre had fallen. Control sera numbering 242 from various sources, including 58 from persons who were histoplasmin-positive and tuberculin-negative, gave entirely negative results.

In the case of proved histoplasmosis there was a close parallel between the results of dermal sensitivity tests and the complement-fixation test.

This serological study offers the hope of a valuable additional means of diagnosis, in the complement-fixation test, and it lends support to the view, based mainly on the evidence of dermal sensitivity to histoplasmin, that histoplasmosis may exist in an undetected, subclinical form. *J. T. Duncan*

HARVEY, N. A. **Progressive Coccidioidomycosis: Report of a Case.** *Ann. Intern. Med.* 1948, Mar., v. 28, No. 3, 651–61, 2 figs. [25 refs.]

"A case of progressive coccidioidomycosis is presented with clinical data and necropsy findings. A generalized coccidioidal peritonitis found at autopsy was apparently caused by the intraperitoneal release of infective material from necrotic liquefying nodules on the surface of the spleen and liver. The complement fixing antibodies never gave a positive test in dilutions greater than 1 : 8, and the patient became anergic to intradermal injections of coccidioidin (1 : 100 dil.) in the terminal stages of the disease. A total of 6,260,000 units of penicillin was given with no demonstrably beneficial clinical effect. Many analogies can be drawn between coccidioidomycosis and tuberculosis. A brief discussion of some aspects of the disease is presented."

FURTADO, T. A. & PELLEGRINO, J. A terapêutica da blastomicose Sul-Americana, ensaios "in vitro" com a estreptomicina. [**Treatment of South-American Blastomycosis. Trial of Streptomycin "in vitro".**] *Brasil-Medico.* 1948, Feb. 21 & 28, v. 52, Nos. 8/9, 54–6. [20 refs.] English summary.

The authors show, by references to the literature, the unsatisfactoriness of the treatment of *Paracoccidioides brasiliensis* infections. They mention local injection of 10 per cent. sodium iodide by Magalhães, methylene blue by Pupo, these same two drugs with sodium cacodylate by Prado, and the varying results recorded of these; the failure of tartar emetic, gonacrine, trypaflavine, arsenicals, sulphapyridine and other sulphonamide drugs. Tyrothricin was favourably reported upon from *in vitro* experiments by Lacaz and Cury, but *in vivo* this could be used locally only because parenterally it was toxic and haemolytic. Now, the authors have tested streptomycin in dilutions from 500 microgrammes to 1 microgramme per cc. on cultures in Sabouraud glucose. Twelve days later growth had been inhibited in the two strongest, partial in the 300 per cc., but not in the others and even with the first two growth took place unimpaired on transfer to fresh medium. The action is, therefore, fungistatic only, and not fungicidal. *H. Harold Scott*

BROCKMAN, D. D. **The *in vitro* Effect of Atabrine on *Cryptococcus neoformans*.** *Amer. J. Trop. Med.* 1948, Mar., v. 28, No. 2, 295–7. [11 refs.]

"Atabrine is fungicidal *in vitro* at concentrations of 25 to 50 mgm. per cent. and fungistatic at 3 to 25 mgm. per cent. for *C. neoformans*. Toxic reactions are obtained with much lower plasma or tissue concentrations. Atabrine is, therefore, of little therapeutic value in cryptococcus infections."

TROPICAL OPHTHALMOLOGY

A Review of Recent Articles. L*.

Parasitic conditions.—A case of Trombiculid mites on the eyelid is described by Boase[1]. The skin of the lash-bearing area of the left upper eyelid presented a reddish powdery appearance. At the first glance this was thought to be red murram dust or some form of native medicinal powder, but on closer examination the dots were seen to be uniform in size, individually of a bright red colour, and evidently red mites. On identification, these proved to be the larvae of the genus *Trombicula*. This genus is the vector of scrub typhus in South-East Asia. The evidence in this case suggests that infestation occurred in the Ankole district of South-West Uganda.

Complete up-to-date literature of ocular sporotrichosis is reviewed by Gordon[2]. Forty-eight cases have been reported in the world literature. Apparently in 34 of these cases, the ocular disease was primary and in 14 secondary to involvement elsewhere in the body. In two of these cases the diagnosis was in question. Of the 48 cases, 10 have occurred in the United States of America and the majority of the remainder in France.

The disease in the eye most commonly manifests itself as ulcers of the lids and conjunctivae. These tend to begin as large subcutaneous gummas and break down to form ulcers. The latter are deep and may even develop in the bony walls of the orbit. The eyeball itself can be implicated in three ways—by direct trauma; by direct extension, or by the blood stream.

The author's case was in a woman aged 48 years, who came to the eye clinic complaining of a " sore " on her upper eyelid. There was no definite history of trauma, but about a week prior to the onset she had been working in her garden among poinsettias. There were marked swelling and redness of the eyelid with a granulation ulcer in the centre. The globe and the lachrymal apparatus were not involved. A culture on Sabourand's medium was made from the material taken by aspiration from a nodule near to the ulcer. This five days later revealed *Sporotrichum schenckii*. The patient was treated with a saturated solution of potassium iodide. The initial dose was 10 drops four times a day. This dose was gradually increased up to 25 drops four times a day, and she responded well to treatment. The average period of medication is from one month to six weeks.

Trachoma.—The treatment of 600 cases of trachoma by sub-conjunctival injections of sulphonamide is discussed by Bierent[3]. These comprised the very early cases, those in the follicular stage, those with active corneal complications, and those with scar tissue formation. The results were excellent.

He has formed the following conclusions :—The accompanying conjunctivitis rapidly disappears. The usual distressing symptoms quickly improve or disappear, the follicles on the tarsal conjunctiva smooth down and become less prominent. In corneal trachoma the improvement is very marked and rapid. Ulcers and abscess of the cornea with hypopyon begin to improve after the first injection, the cornea losing its angry appearance with rapid clearing up of the zone of infiltration and cicatrization occurring after a few days. Pannus crassus becomes less intense and quickly smoothes down and retrogresses. Diffuse opacities of the cornea become less in extent, the cornea becoming more

* For the 49th of this Series see Vol. 45, pp. 1093–1095.

[1] Boase, A. J. Trombiculid Mites on Eyelid. *East African Med. J.* 1947, Oct., v. 24 No. 10, 363.

[2] Gordon, D. M. Ocular Sporotrichosis. Report of a Case. *Arch. Ophthalmology.* 1947, Jan., v. 37, No. 1, 56–72, 3 figs. (1 in colour). [60 refs.]

[3] Bierent, P. Essais de traitement du trachome (600 cas) par des injections sous-conjonctivales de sulfamidothiourée. *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 7/8, 277–84.

transparent with considerable improvement of vision in many cases. Those cases with xerosis and infections of the uveal tract show no improvement.

In the ordinary cases, there are no contra-indications to the use of the drug. Pain sometimes occurs, especially after the first injection and occasionally a slight haemorrhage appears after the injection.

The dosage recommended is ¾ to 1 cc. of the solution. [No mention is made of the exact composition of sulphonamide used or the strength of the solution.]

Leprosy.—The effect of Grenz rays on leprous infiltrations on the anterior portions of the eyeball is discussed by SAGHER and MITERSTEIN[4]. Lepromas on the bulbar conjunctiva close to the limbus are somewhat amenable to local therapy, unless the process has penetrated too far into the eye or originates from the ciliary body. The usual treatment of these lepromas consists in the application of solid carbon dioxide, the local injection of various drugs, and surgical measures. In previous experiments with irradiation, it was found that cutaneous lepromas were noticeably affected by the Grenz rays and the results were fairly good.

The authors treated 6 patients in whom there were lepromatous changes in the anterior segments of the eyeball. Three practically sightless eyes were first exposed to these rays and in all 3 patients the lepromas became reduced in size or disappeared completely. When the Grenz rays were employed on the eyes of 3 additional patients which presented lepromas with fairly good vision, two eyes exhibited a favourable response, and in the third the lepromatous part became quiescent or even slightly flatter, while the surrounding parts presented rapid growth of new lepromas. The voltage of the rays used ranged from 6 to 14 kilovolts, which is equivalent to half value layers of 0·021 to 0·031 mm. of aluminium. The most effective doses applied at one sitting were from 700 to 1,200 k, the total amount varying from 5,500 to 11,600 k.

These large doses could be applied safely to the external tissues of the eye, because the sensitivity of such tissues to rays is lower than that of the skin. No damage to the cornea, lens or deeper structures of the eye was noted, so far as this could be determined on the basis of observations extending over a period of between two and four years.

Optic neuritis.—A case of tryparsamide optic neuritis treated by 2,3 dimercaptopropanol (BAL) is reported by FRIEDENBERG[5]. The case was one of tabes dorsalis due to syphilis which was treated for six months with intramuscular injections of sodium iodobismuthite and a course of penicillin. These were followed by two intravenous injections of 0·7 gm. and 1·0 gm. of tryparsamide at a week's interval between the injections. Two days after the second injection the patient complained that he could not see the sidewalk when walking. Examination confirmed the loss of the inferior visual fields and that he was suffering from optic neuritis. He was at once put on BAL therapy. The first two days he was given 300 mgm. twice daily and the following eight days he was given 300 mgm. daily with the exception of the fifth day, when 400 mgm. were given. Several hours after this injection he complained of paraesthesias in the left side of his neck and jaw. This lasted about one hour. Vision returned nine days after BAL therapy was stopped. On examination six months later, the visual fields showed great improvement and the acuity of vision remained normal. The author is of opinion that the unusually rapid return of vision was probably due to the prompt use of BAL as soon as the patient complained of visual disturbance.

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[4] SAGHER, F. & MITERSTEIN, B. Effect of Grenz Rays on Leprous Infiltrations. III. Response of Lesions of the Anterior Portions of the Eyeball. *Arch. Ophthalmology.* 1947, July, v. 38, No. 1, 78–88, 1 fig. [13 refs.]

[5] FRIEDENBERG, S. Tryparsamide Optic Neuritis treated by 2,3 Dimercaptopropanol (BAL). *J. Amer. Med. Ass.* 1947, Dec. 20, v. 135, No. 16, 1072.

[Pentavalent arsenical compounds, chiefly tryparsamide and atoxyl, are used in trypanosomiasis as well as in cerebrospinal syphilis and carry certain risks, the most important of which is damage to the retina and visual pathway.]

E. O'G. Kirwan

HEAT STROKE AND ALLIED CONDITIONS

RAO, M. N. **Some Physiological Problems in Tropical Life.** *J. Indian Med. Ass.* 1947, Aug., v. 16, No. 11, 375–81, 6 figs. [24 refs.]

BRUNT, D. **Some Physical Aspects of the Heat Balance of the Human Body.** Reprinted from *Proc. Physical Soc.* 1947, v. 59, 713–26, 6 figs. [10 refs.]

This paper is mainly based on the experimental work of Winslow and his colleagues of the Pierce Laboratory of Hygiene, Newhaven, U.S.A. Some of the results of that work are summarized. The author shows that the combined convective and evaporative heat losses from the body are proportional to the difference between the total heat content of air saturated at the mean skin temperature, and the total heat content of the ambient air. The upper limit of temperature and humidity for the nude man is given in terms of the temperature of radiating surfaces, the total heat content of the air and the air velocity. This equation requires that the mean skin temperature is known, but it is said that there are available sufficient observations to enable a reasonably accurate figure for that skin temperature to be estimated for given rates of physical effort.

A diagram is given which shows the limiting combinations of wet-bulb temperature and temperature of radiating surfaces for nude subjects in various degrees of physical activity and with varying rates of air movement. The diagram also shows, for various conditions, rates at which sweat must be evaporated to maintain heat balance. These computations are compared with experimental data obtained by various research workers, and they are shown to agree very well.

A further diagram gives a tentative classification of climates, in terms of air temperature and relative humidity. Limiting conditions are shown for :—

(*a*) Nude persons resting in still air ;
(*b*) Nude persons resting in air moving at 200 feet per minute ;
(*c*) Clothed persons resting in sunshine ;
(*d*) Clothed persons walking at 3 miles per hour.

The limits shown for nude persons are those above which heat-stroke is likely to occur, while those of clothed persons are the conditions at which about one-third of the skin area is wet with sweat.

T. Bedford

MISCELLANEOUS DISEASES

KAUER, J. T. **Medical Experiences in Luzon P.O.W. Camp No. 1.** *Bull. U.S. Army Med. Dept.* 1948, Apr., v. 8, No. 4, 302–9.

GUIMARÃES, F. N. Doenças encontradas nos romeiros de Bom Jesus de Lapa, Bahia. [**Diseases observed among Pilgrims to Bom Jesus da Lapa, Bahia.**] *Mem. Inst. Oswaldo Cruz.* 1947, Mar., v. 45, No. 1, 211–51, 1 map & 30 figs.

[An account of what must have been a most interesting study.] The author, in July 1946, was sent by the Director of the Institute Oswaldo Cruz

as one of a team to investigate disease among pilgrims attending " one of the most typical and traditional fanatico-religious festivals in Brazil", that of Bom Jesus da Lapa, Bahia. Others sent were a bacteriologist to study trachoma, a hygienist to study the general sanitation, and ophthalmologists to study the clinical side of trachoma and other eye-conditions. The author gives an account of the festival and the activities of those attending it. This is worth reading from an ethnological point of view, but this part is beyond the scope of an abstract on the diseases he found. *Malaria* is endemic in the district; the blood of 28 persons with fever was examined and 7 were positive, 6 with splenomegaly; 4 had *P. vivax*, 3 *falciparum*. Among the mendicants especially *cutaneous leishmaniasis* was seen and photographs reproduced show the lesions clearly. *Ulcers* were common, some with Vincent's spirochaete and fusiform organisms. No case of *Chagas's* disease was seen, though one woman had tachycardia and extra-systoles and knew of the " barbeiro". *Helminthiasis* was looked for in a few persons only, and *Necator americanus*, *Ascaris lumbricoides* and *Trichuris trichiura* were noticed to be present, and ova of *S. mansoni* were seen in one who came from Medina in Minas Gerais. *E. histolytica* was observed in one patient and *Chilomastix mesnili* in two [but only 15 samples of faeces were examined]. *Yaws* was seen and a photograph of the patient is reproduced. Other diseases were *goitre*, several cases, and in two or three members of a family, *trachoma*, *neurofibromatosis* (von Recklinghausen's disease), *filariasis* with elephantiasis, *venereal diseases* and, in the words of the author, Beggars' Street (*rua dos mendigos*) was a " veritable museum of teratology "—note is made of seeing cases of achondroplasia, hydrocephalus, dwarfism, microcephaly, etc. Many photographs of interest illustrating the locality, scenes at the festival and the lesions referred to above are appended to the article. *H. Harold Scott*

Sicé, A. La pathologie tropicale et son évolution. [**The Development of the Pathology of Tropical Diseases.**] *Acta Tropica*. Basle. 1948, v. 5, No. 1, 57–77.

Lovett-Campbell, A. C. **Splenectomy in the Tropics.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Jan., v. 41, No. 4, 567–73.

Surprisingly slight trauma can rupture a congested malarial spleen, yet accident cases comprise only a minority of splenectomies undertaken in West Africa. The majority are performed for the relief of incessant pain and discomfort due to the dragging of an enlarged spleen on its attachments to adjacent organs in persons reduced to chronic ill-health by various tropical affections implicating the spleen. A preliminary course of antimalarial therapy often reduces its size appreciably and during treatment the retracting spleen often causes characteristic aggravation of pain; the treatment of co-existing helminthiasis, amoebiasis, etc., is carried out during this period. Spinal anaesthesia with percaine, supplemented by intravenous cyclonal sodium, gave satisfactory relaxation in all cases. A paramedian or rectus-splitting incision, with an upper trans-rectus incision where necessary, allowed comfortable access to even the largest spleen. Thorough separation of all adhesions to the costo-diaphragmatic peritoneum on the convex surface must precede any attempt to deal with the pedicle; this phase produces the most shock and should be carried out rapidly, bleeding points being controlled by hot packs. Only after the spleen has been rendered completely mobile can the whole pedicle be identified and safely ligated. The tail of the pancreas and greater curve of the stomach are usually densely enveloped in compressed omental folds, which are firmly adherent to the spleen. These points are exemplified by seven case histories, in two of which

splenectomy was done for traumatic rupture and in five for splenomegaly. In both the patients with traumatic rupture a quiescent period, lasting in one case for three days, preceded the onset of acute symptoms.

W. L. Harnett

ELMES, B. G. T. & BALDWIN, R. B. T. **Malignant Disease in Nigeria: an Analysis of a Thousand Tumours.** *Ann. Trop. Med. & Parasit.* 1947, Dec., v. 41, Nos. 3/4, 321–8, 4 figs. on 2 pls. [13 refs.] [Summary appears also in *Bulletin of Hygiene.*]

In a paper published in 1934 and abstracted in this *Bulletin* [1935, v. 32, 522], SMITH & ELMES gave a detailed analysis of 500 consecutive malignant tumours which had arisen in Nigerian Africans and had been submitted to pathologists in that country for identification. The present paper is a summary of 1,000 additional tumours from the same source. The tumours correspond in nature and incidence fairly closely with those recorded in the earlier paper. The youth of the patients is again noticeable, 248 of the 1,000 having been under thirty years old. Of all the tumours 8·1 per cent. began in the liver and were associated with subacute necrosis and cirrhosis of the Laennec type. Attention is specially drawn to those conditions in which the causation is not entirely obscure. Among these, besides the liver cancers, which are largely due to erroneous feeding, are many epitheliomas growing in leg-ulcers, five cases of scrotal cancer, and ten of cancer of the penis. Of 18 instances of malignant disease of the bladder, only four were accompanied by *Schistosoma haematobium* infection, despite the frequency of this malady in Nigeria. Notable features among the thousand tumours analysed are the relative frequency of melanoma (6·2 per cent.), mixed salivary tumour (4·9 per cent.) and adamantinoma (1·8 per cent.). The paper, though brief, contains several other items of interest and should be read in the original.

Harold Burrows

PROTOZOOLOGY: GENERAL

KEAN, B. H. & GROCOTT, R. G. **Congenital Toxoplasmosis.** *J. Amer. Med. Ass.* 1948, Jan. 10, v. 136, No. 2, 104–8, 11 figs. [Refs. in footnotes.]

The case described was in an infant prematurely born after 6½ to 7 months of pregnancy. The infant died 10½ hours after birth. A post mortem was performed 31 hours after death, the body having been kept in the refrigerator at a temperature of 32 to 38°F. The brain was a collapsed gelatinous mass and was covered by haemorrhagic leptomeninges. Histologically, areas of focal necrosis with extensive deposition of calcium salts occurred. The eye showed extensive chorio-retinitis. Toxoplasma were found in the brain, eye and many other organs. Inoculated with brain material, guineapigs acquired an infection which was maintained by sub-inoculations. Attempts to demonstrate a latent infection in the mother failed, but a serological protection test was not carried out. This is the first case of congenital toxoplasmosis to be described from Panama.

C. M. Wenyon

RUCHMAN, I. **Occurrence of Toxoplasma Neutralizing Antibodies in various Disease Conditions.** *J. Lab. & Clin. Med.* 1948, Jan., v. 33, No. 1, 87–95. [13 refs.]

The toxoplasma neutralization test of SABIN was employed to determine the presence of antibodies in various diseases. Of the sera from 72 selected individuals, twenty were positive, forty-eight negative and four doubtful. There

was a high incidence of positive sera amongst children showing signs of congenitally acquired toxoplasmosis—convulsions or other signs of central nervous system involvement and hydrocephalus or microcephalus when these were associated with chorioretinitis or cerebral calcification. The blood of the mothers of such patients regularly showed antibodies. Antibodies were also found in a child with prolonged encephalitis and in two adults with mental disturbances. The antibodies persist in the blood stream for at least five years. Many conditions of obscure aetiology failed to show the presence of antibodies. *C. M. Wenyon*

ENTOMOLOGY AND INSECTICIDES: GENERAL

MACKERRAS, I. M. **The Jackson Lecture. Australia's Contribution to our Knowledge of Insect-borne Disease.** *Med. J. Australia.* 1948, Feb. 7, v. 1, No. 6, 157–67. [Bibliography.]

The lecture gives a readable general account of the development of our understanding of insect-borne diseases: it pays particular attention to Australian problems and the work carried out in that continent. It gains much because the author has a first-hand knowledge of some parts of the work and also because of the excellent list of selected references. Like many other general papers, it is difficult to summarize.

The author gives a general classification of his subject, pointing out that there are many different types of relationship between the arthropod and the mammal. He then develops the subject historically under three periods. In the first of these, most of the major discoveries were made and the period might be said to be one of zoological observation. So far as Australia is concerned, it started in 1876 with the discovery by Joseph Bancroft of the adult nematode which was called *Filaria bancrofti* by Cobbold. This first period ended at about the year 1900.

During the second period, which occupied the first twenty-five or thirty years of this century, few major discoveries were made except in the life histories of rickettsiae, but results worked out in one area were plotted or confirmed in many other parts of the world, and the sciences of parasitology and medical entomology may be said to have been established. During this period, Australian workers made important contributions to knowledge, particularly the relation to plague, dengue and filariasis. They also carried out most useful surveys of the parasites of Australian vertebrates.

In the third period, which commenced between the world wars, experimental and physiological studies were developed, founded on the earlier observations, so that there was a great elaboration of technique. In medical entomology, ecology and the closely related science of epidemiology began to take a large place. Australian workers covered a wide field. One might perhaps refer particularly to their virus research and that on infections of the typhus group, which became of such importance during the war period. Here the author records with legitimate pride that it was an Australian who brought in the use of the phthalates to kill the *Trombicula* and showed how they could be applied in the field. Outstanding Australian work on many sides of malaria must be familiar to all. It is less well known that when an epidemic resembling dengue appeared in jungles in New Guinea, it was shown that the infections were carried by a jungle mosquito *Aëdes scutellaris*, infected material being taken by air to Australia where the experimental proof was completed.

P. A. Buxton

FERGUSON, M. S. & GRAHAM, O. H. *Phlebotomus* **in New Guinea and Nearby Islands.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1948, Mar., v. 41, No. 5, 679–84, 2 figs.

Adults of *Phlebotomus*, as yet undescribed, were collected from tree holes, trunks and buttresses. For the collection of living sandflies, tobacco smoke was used; later, the Freon aerosol bomb was employed and the flies fell on to a white cloth and died. No *Phlebotomus* were taken in fox-holes or in pill-boxes; fallen trees and light traps yielded none, though other members of the family were sometimes numerous.

A table is given of the data concerning the collections and a map shows where the collections were made. The rôle played by *Phlebotomus* in the transmission of disease was not determined. It is expected that descriptions of these sandflies will be published in due course. *H. S. Leeson*

BRENNAN, J. M. **An Instance of the Apparent Toxicity of Man to Ticks.** *J. Parasitology.* 1947, Dec., v. 33, No. 6, 491–4.

The man to whom this paper relates was apparently perfectly healthy, scrupulously clean, exceptionally hairy, and was not addicted to narcotics or alcohol; his only excess was to drink as many as 20 cups of coffee each day. Adult ticks (*Dermacentor andersoni* and *Amblyomma americanum*), held in contact with his skin (in the antecubital fossa) for some 10–40 minutes, were always rendered immobile; they revived within 24 hours, but never became quite normal. Nymphs of *D. andersoni* held in the same place, or in the closed hand, were killed in 3–10 minutes. Controls on other persons were entirely unaffected.

On the other hand, adult ticks and nymphs applied to parts of the skin free from sweat behaved irregularly; some were affected and others not. Ticks held near the skin but not on it were not affected. It was not possible to collect a quantity of sweat sufficient for a real test, but ticks placed inside a rubber glove worn by the subject of the experiment, and containing a trace of sweat, were not affected; his urine was harmless to them.

The ticks were obviously repelled, as well as intoxicated. It seems likely that there is some substance, presumably associated with the man's sweat, which is both toxic and repellent. The condition is rare, since no suggestion of it was found in 70 volunteers to whom ticks were similarly exposed. If this substance could be isolated, results of far-reaching value might be obtained. *Charles Wilcocks*

HARANT, H. & BAUR, O., Mlle. Sur la présence en France de *Dermacentor niveus* (Neumann, 1897). [**The Presence in France of** *Dermacentor niveus* **(Neumann, 1897).**] *Bull. Soc. Path. Exot.* 1947, v. 40, Nos. 11/12, 465.

The authors found a male specimen of *Dermacentor niveus* on the scapular region of a Mongolian child of 5 who was under treatment in the neighbourhood of Lodève (Hérault). This child had a continuous fever of 39° to 40°C. on the day of examination and on the five following days. No other signs, cutaneous or visceral, were found in the patient.

The common hosts of *D. niveus* are the sheep, camel and wild boar: it is possible that the tick was dropped from some animal in the meadows where the child was accustomed to play. It is evident that, although as far as the authors are aware, this species has not been reported from France before, it does occur, can attach itself to man and had a possible bearing on the febrile attack of the child who accidently acquired it.

The authors assume that *D. niveus* cannot be regarded as a simple variety of *D. reticulatus* (Fabricius, 1794) a species well known in Europe and commonly known to-day as *D. marginatus* (Sulzer, 1776).

H. J. O'D. Burke-Gaffney

GARNHAM, P. C. C. **The New Insecticides.** *East African Med. J.* 1948, Jan., v. 25, No. 1, 5–10.

This paper discusses the use of DDT and Gammexane and particularly describes experiments carried out in recent years in East Africa in the control of insect borne diseases. The use of the newer insecticides in the control of malaria, relapsing fever and onchocerciasis is described ; the results of relevant experiments have already been abstracted in this *Bulletin* from time to time. The author also gives a brief description of the use of these insecticides in the control of *Aëdes aegypti* and of common domestic pests.

H. J. O'D. Burke-Gaffney

DRESDEN, D. & KRIJGSMAN, B. J. **Experiments on the Physiological Action of Contact Insecticides.** *Bull. Entom. Res.* 1948, Feb., v. 38, Pt. 4, 575–8. [12 refs.]

The toxicity of an insecticide to an insect or vertebrate can be determined from external applications or by injection into the body cavity. Data obtained by other workers are summarized and further results obtained by the authors with a cockroach, a stick insect and a frog are tabulated. According to these comparisons, the *internal* toxicity of DDT, Gammexane and Rotenone are of the same order to vertebrates and to insects. But the vertebrates require much higher external doses, showing that their skins are effective barriers to this type of poison, whereas the insect cuticle is readily penetrated.

The toxicity to *Periplaneta* of the various isomers of hexachlorcyclohexane was investigated. It was found that, even after injection, the *gamma* isomer is outstandingly effective ; its toxicity, therefore, is not due merely to its ability to penetrate the cuticle.

In view of the suggested connexion between Gammexane poisoning and meso-inositol, tests were made in which cockroaches were injected with both separately and with various mixtures. The inositol (which was itself innocuous) showed no sign of reducing the toxicity of the Gammexane.

J. R. Busvine

JONES, B. M. **Preliminary Tests of DDT Emulsion Concentrates.** *Bull. Entom. Res.* 1948, Feb., v. 38, Pt. 4, 585–90, 2 figs.

The following emulsion concentrates were tested ; Nos. 1, 3 and 4 " soluble oil " type ; No. 2 " mayonnaise " type. Nos. 1 and 2 had solvent naphtha as a solvent for the DDT, whereas Nos. 3 and 4 had a toluene-turpentine mixture. The DDT content of these concentrates ranged from 23 to 30 per cent.

A simple test of stability was to prepare 1 per cent. DDT emulsions from all concentrates and to observe how soon the emulsions would break. Nos. 1 and 2 were stable for twenty-four hours, but Nos. 3 and 4 separated into two layers in thirty minutes and had broken in twenty-four hours. The initial separation of Nos. 3 and 4 was delayed by the normal agitation of a man using a knapsack sprayer. Attempts to prepare 1 per cent. dilutions with salt water (4·5 per cent. salinity) were only successful with the " mayonnaise " formula.

As a small field trial, two rooms were sprayed with emulsions diluted to 5 per cent. from concentrates Nos. 1 and 2, to give about 200 mgm. DDT per sq. ft. Mosquitoes (*Armigeres obturbans* and *Culex gelidus*) were liberated in the

treated rooms, for various periods, at intervals up to sixty days, after treatment. The exposure necessary to produce 100 per cent. kill rose from about an hour to ten hours, but the loss of activity was not more rapid than with a kerosene-DDT treatment. *J. R. Busvine*

BRENNAN, J. M. **Field Tests with Tick Repellents.** *Pub. Health Rep.* Wash. 1948, Mar. 12, v. 63, No. 11, 339–46.

Field trials of tick repellents were arranged by the Rocky Mountain Laboratory, Hamilton, Montana, in collaboration with the U.S. Army. Men wearing fatigue kit were exposed to heavy attacks of *Amblyomma americanum* for about four hours per day for eight days in one trial and for ten days in another trial. The uniforms had been impregnated with one or two ounces of the various repellents (a pair for each treatment and four controls). Ticks acquired were removed and counted at intervals. The results are a little difficult to interpret because some of the treatments were more effective than others at first, but did not last so well. Some were only highly effective against nymphal ticks while others were also good against the adults. However the following conclusions seem justified :—

From the standpoint of maximum repellency, butylacetanilide and benzyl cyclohexanol were first and second in all tests. Butylacetanilide also showed indications of promise as a mite (chigger) repellent. Although there are no data regarding its toxicity to mammals, it is known that related compounds are harmless. There were no adverse reactions in the soldiers who wore the impregnated clothing.

Benzyl benzoate and dimethyl phthalate were also included in the tests. They gave rather erratic results, especially against adults, but their repellence was fairly high and in view of their availability and safety, they should be used against ticks at present.

Dibutyl phthalate and the "6 : 2 : 2" mixture gave rather poor results against ticks. [The "6 : 2 : 2" mixture contains 60 per cent. Dimethyl phthalate, 20 per cent. Indalone, 20 per cent. 2-ethyl-1 : 3-hexanediol.]

J. R. Busvine

REPORTS, SURVEYS AND MISCELLANEOUS PAPERS

ROSS INSTITUTE OF TROPICAL HYGIENE. LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE. **Report of the Eighteenth Meeting of the Ross Institute Industrial Advisory Committee, 6th January, 1948.** [WIGGLESWORTH, A., Chairman]. 23 pp., 1 diagram.

This is an account of a meeting at which the chairman, Mr. Wigglesworth, referred to the opening of the new branch of the Ross Institute at Tanga, in Tanganyika Territory. A paper was read by Dr. TREDRE on the East African labourer, in which he remarked that 90,000 men are employed on estates in Tanganyika, half of them round Tanga. These men suffer much from malaria, hookworm infestation and anaemia, and are often underfed. A haemoglobin content of only 60–70 per cent. is not uncommon in men who make no complaint of illness. Although the Government have laid down a minimum ration of 2,800 Calories for labourers, it is not possible to be sure that each man gets the amount in full, or prepares the food adequately for consumption.

Papers on the eradication of *Simulium* from streams in Kenya, by the use of DDT, and on mass treatment in the control of schistosomiasis in Southern Rhodesia, were read by Dr. GARNHAM and Mr. ALVES. Papers on these subjects

have already been reviewed in this *Bulletin*. Alves makes the important point that the opening up of African water supplies for hydro-electric, irrigation or even domestic use, will mean corresponding extension of the area in which the schistosome-bearing snails are to be found, unless the engineers seek the advice of public health workers from the start. [It would be impossible to over-rate the importance of this.] *Charles Wilcocks*

COLONIAL OFFICE. **Inter-University Council for Higher Education in the Colonies. Report 1946–47** [IRVINE, J. C., Chairman]. Cmd. 7331. 12 pp. 1948. London: H.M. Stationery Office. [*3d.*]

GABUS, J. Organisation et premiers résultats de la Mission ethnographique chez les Touaregs soudanais du 26 décembre 1946 au 10 mars 1947. [**Preliminary Report of the Ethnographic Mission to the Tuaregs of the French Sudan in 1946–47.**] *Acta Tropica*. Basle. 1948, v. 5, No. 1, 1–56, 5 maps, 11 figs. & 16 photos.

INDIA. **Annual Report of the Public Health Commissioner with the Government of India for 1945** [COTTER, E.]. pp. iv+91, 2 folding maps & 8 charts. 1947. Delhi: Manager of Publications. [*Annas* 14 or 1*s.* 3*d.*]

This report is described as being more or less on the same lines as those of the years immediately preceding the war; it contains considerably more information than was provided for the years 1941–1944; but, on the other hand, certain items are omitted because they have already appeared in a preliminary note published earlier in the year (1947).

In spite of the war, some progress can be reported: for example, certain provinces introduced compulsory inoculation against cholera for persons desiring to attend the religious "fairs" which had hitherto played so great a part in disseminating infection.

The birth rate for 1945 was 27·3 *per mille* against 25·4 in 1944 and 32 to 34·5 during the five years 1937–1941.

The death rate was 21·5 per mille against 24·1 in the previous year and 21·1 to 24·3 during the period 1937–1941. In Orissa the death rate was slightly higher than the birth rate, and in the Central Provinces both rates were about 39 per mille. In the Punjab the birth rate (about 37) was nearly twice as high as the death rate (19·5).

The infant-mortality rate was 150·9, the lowest ever recorded, but there again there are surprising differences; for example, the rate in the central Provinces was 256·6 whereas in Bihar it was less than 100 although in the latter province the total death rate was nearly the same as for British India as a whole.

It must be understood that all the vital statistics for India are quite unreliable; local checks have repeatedly shown that many births and deaths, especially infant deaths, have not been reported. It is disquieting to find that in a Health Unit in Madras dealing with a population of about 50,000, the infant-mortality rate was 236 despite the fact that for several years the area had been provided with a special health staff, including trained midwives.

In several provinces deaths from cholera and smallpox were more numerous than for many years past, but although these diseases attract special attention because of their dramatic nature, taken together they were responsible for only about one-fifteenth of the deaths in British India as a whole. Readers of the report will be surprised at the statement that Bengal was "only mildly" affected by cholera, the deaths from the disease having been 32,550.

Vaccination against cholera was practised on a large scale in most of the affected areas; the numbers of inoculations were: in Bengal 7½ million;

in Bihar nearly 6 million; in the Central Provinces, Bombay, and Madras about 2 million each.

The incidence of plague continued to decline except in Bombay Province where there were 11,779 deaths against 2,514 in 1944. The preventive value of DDT, which was released for use during the year, was being investigated.

Malaria was not unusually prevalent during the year. It is interesting to find that "although there is some prejudice in favour of quinine, mepacrine is now becoming quite popular". Fears are expressed that control by DDT may be too costly for general adoption.

As usual the information regarding the prevalence of the enteric group of fevers is meagre, but it is stated as being "fairly certain" that no epidemic occurred during the year. [The most likely explanation of the absence of epidemics in India is that infection is so widespread that most of the children suffer from attacks which are regarded as "simple fever" so that the adult population are relatively immune.]

Pulmonary tuberculosis is believed to cause 500,000 to 800,000 deaths every year, but accurate information on the subject is not yet available; chronic malnutrition is mentioned as one of the chief factors contributing to the prevalence of this as well as of most of the other diseases included under the headings "fevers" and "all other causes" which are shown as the causes of about three-fourths of all the deaths that occur in India.

Kala azar is believed to have increased slightly in Bengal and Assam during the year; this is the one disease in India that is being kept under a reasonable degree of control, thanks to the popularity of the effective treatment available in the endemic areas.

A brief summary is given of the important Report of the Health Survey and Development Committee which was completed during the year [see this *Bulletin*, 1947, v. 44, 252]. Strangely enough no mention is made of the remarkable fact that all but two of the 25 members of this fully representative Committee subscribed to the view that "the growth of population will become an increasingly serious problem" and that even if economic productivity is developed to the greatest possible degree "uncontrolled growth of population must, as far as we can see, outstrip the productive capacity of the country." This view was reached by the Committee after a long and careful study of the available evidence; its bearing on the public-health policies of all the crowded and backward countries of the world is of crucial importance.

The rest of the present report is on the usual lines; it deals with the work of the official and voluntary health organizations and with medical research which continues to progress far more rapidly than the practical application of the discoveries made by the investigators. The graphs which illustrate the report are very helpful, though necessarily they are no more reliable than the statistics on which they are based. *John W. D. Megaw*

INDIA. **Statistical Appendices to Annual Reports of the Public Health Commissioner with the Government of India for the Period 1940–1944.** pp. ii+177. 1947. Simla: Manager, Government of India Press for Manager of Publications, Delhi. [*Rs.* 2 *Annas* 8.]

EAST AFRICAN MED. J. 1948, Jan., v. 25, No. 1, 29–73. **The Case for the Appointment of a Royal Commission on Health and Population in His Majesty's Dependencies in Africa. Memorandum by the Council of the Kenya Branch of the British Medical Association.**

The authors of this long document evidently feel strongly that the time has now come (and is probably overdue) when much more radical and energetic steps must be taken to promote the welfare of the whole population of East

Africa, than have hitherto been considered. They base their argument on the fact that the population is increasing at a rapid rate (some 12 millions in 1936 increasing at a not impossible rate of 2·3 per cent. per annum would exceed 18 millions in 1956), and on the other fact that the fertility of the soil is being reduced, largely by inefficient agricultural methods. This problem is by no means peculiar to Africa, and is more and more engaging the attention of medical men and administrators in various parts of the world [see this *Bulletin*, 1945, v. 42, 506, 507 ; 1946, v. 43, 81, 603 ; 1947, v. 44, 252 ; 1948, v. 45, 215]. The case made by the authors is very strong indeed, though the reader may think that it would have been even more telling if it had been made much more succinctly.

The memorandum is divided into a prefatory note and two parts. Part I contains the proposal for a Royal Commission, and a discussion of the modern conception of health, which is based very largely on the ideas inherent in the Report of the National Health Services Commission, Union of South Africa, 1944, and on the papers by PATERSON on a population policy for East Africa [see this *Bulletin*, 1948, v. 45, 124].

Part II contains a section on planning, in which the authors stress the fact that information on most of the matters relevant to schemes for improvement, is scanty and inaccurate. There is reason to believe that the health of the people of East Africa is deteriorating, and it is known that some parts of the country are so overcrowded that thinning of the population is becoming urgently necessary. The position will probably continue to deteriorate unless a bold effort is made to cope with it. Quotations are given from speeches and reports made by government officials, which support this contention and which show that the position is known in official quarters. The old structure of African society, based on family units and unlimited land, is breaking down in the face of industry, poverty of the soil and crowding.

The health services are inadequate, and must eventually be supported largely by qualified and trained Africans, but in the meantime such medical and public health services as are possible must be developed—but a long-term plan is needed.

The argument for a plan for East Africa is very strong ; the suggestion of a Royal Commission may be the best approach to a situation so difficult that it may well be beyond the power of the countries chiefly concerned to deal with it unaided. *Charles Wilcocks*

COONOOR. **Pasteur Institute of Southern India, Coonoor. Annual Report of the Director together with the Fortieth Annual Report of the Central Committee of the Pasteur Institute Association 1946–47.** 50 pp., 1 chart. 1947. Madras : Diocesan Press.

The Pasteur Institute of Southern India is a private institution founded in 1906 and governed by a representative committee of its own. While its main object is to provide measures for the prevention of rabies and to undertake research and propaganda in connexion with that disease, it also provides for general laboratory and research work in that part of India. The Institute also gives facilities for research financed from other sources ; the Nutrition Research Laboratories of the Indian Research Fund Association has worked there for many years and the Southern India Branch of the Research Section of the Malaria Institute of India worked there during 1946.

Much of the report is naturally devoted to reports and statistical statements regarding rabies and antirabic measures. It is noted that 20,601 patients were treated at the Institute and at Subsidiary Treatment Centres during the year.

The antirabic vaccine used was a 5 per cent. suspension of sheep brain (Paris strain of fixed virus) in carbol-saline prepared by Semple's method.

In the Institute itself, 370 persons received a complete course of antirabic treatment and 32 received incomplete courses: among this total of 402 there were only 2 deaths.

Routine laboratory examinations amounting to 3,300 were carried out for local hospitals and practitioners.

Research work, in addition to that on rabies, included investigations into the action of heparin on snake venom, tropical eosinophilia and haemoglobin values in South India.

The Nutrition Research Laboratories studied the Vitamin B complex, hydrogenated oils, the comparative value of milk and curds, phosphatase, metabolic disorders of the liver and experimental lathyrism. Two nutrition classes were held in 1947, one for medical and science graduates and the other for nursing, social and welfare workers.

Most of the research work referred to above has been published and abstracted in this *Bulletin*. *H. J. O'D. Burke-Gaffney*

UNITED STATES NAV. MED. BULL. 1948, Mar.–Apr., v. 48, No. 2, 258–62. **General Information regarding Tropical Hygiene and living in the Tropics.**

BOOK REVIEW

DE SOUZA LIMA, Lauro & DE SOUZA CAMPOS, Nelson. **Lepra tuberculoide. Estudo clínico histopatológico.** [Clinical and Histopathological Study of Tuberculoid Leprosy.] 298 pp., 109 figs. 1947. São Paulo: Editora Renascença S.A.

This book begins with a quotation taken by RABELLO from W. HUGHES'S paper on Tuberculoid Leprosy in the *Transactions of the Royal Society of Tropical Medicine and Hygiene* (1938, v. 31, 383) [see this *Bulletin*, 1938, v. 35, 290, 547; 1939, v. 36, 239] to the effect that no aspect of leprosy has attracted in recent years so much attention as the tuberculoid form, and that the recognition of it constitutes probably the most important advance in the study of the disease since Hansen discovered the organism in 1874. Tuberculoid leprosy is generally benign, it is practically non-contagious and therefore, in the majority of cases, there is no need for segregation; it originates in highly infected localities and is a true vaccination and thus "increase in the number of cases of tuberculoid leprosy leads us to hope for a proportionate decline in the severity of the endemic disease."

This book, in which the authors have collated and discussed all that is known of this form of leprosy, is a full account based on their observation of nearly 1,000 cases. They describe the evolutionary stages with illustrative photographs, the minute histological changes in tissues obtained for section by biopsy, the bacterioscopy, and the Mitsuda reaction; they give clinical descriptions of cases, and comment on research for the sources of contagion in the histories of antecedents and by examination of collaterals and descendents.

In order to set out more clearly the clinical picture and the histological features, the authors describe by way of preliminary the general characters of this form of the disease, and in Chapter I they define tuberculoid leprosy in general terms, its different forms and its position in the general clinical picture;

they discuss the Cairo and South American classifications, giving their reasons for discarding the former and adopting the latter, and indicating that tuberculoid leprosy is a distinct and well-characterized form of the disease, with lesions of the skin, or of the nerves, or of both. There follows a study of the cutaneous lesions with suggestions for a more rational classification, and a review of the classifications of Tisseuil, of Ota and Sato, of Leffrou and Des Essarts and others.

Next comes a description of the histological picture of a " pretuberculoid focus " with marked lymphocytic reaction passing on to the sarcoid and lupoid types and an account of the clinical characters, the nodular, papular, macular and " geographical " subtypes, the colour, localization, changes of sensation, degree of infiltration, the finding of (or, rather, the search for but frequent failure to find) bacteria and the results of the Mitsuda reaction in the different clinical subforms. Succeeding chapters are devoted to dealing more fully with each of the types mentioned, starting with the " figured leprides," *i.e.* lesions with an infiltrated border, papular, reddish to violet in colour (or perhaps hypochromic) and sometimes with a fine desquamation. These are the same as those designated by Ota and Sato as " trichophytoid leprides." The illustrations reproduced show the lesions very clearly. The subject is dealt with under the headings of morphology of the centre and of the edges, the results of examination for bacilli, the Mitsuda reaction, the minute pathological histology of different parts of the lesion, and the prognosis. Cases are subdivided into groups according to the stage of evolution of the lesions into incipient, fully developed and retrogressing.

The nodular type comes next under consideration. This is more common in the young, and the lesions are of a lupoid character, a " tuberculoid granuloma." In this group the Mitsuda reaction is strongly positive, the nervous system is rarely, if ever, involved (at least not obviously) and there is a tendency to retrogression and cicatrization ; in short, it is the most benign form of tuberculoid leprosy. The commonest single sites are, in order, the face, thigh, gluteal region, and forearm. Bacteria are few or absent. In this, as in other chapters, the same lines are followed—a clinical study with notes of cases, localization, results of bacterioscopy and of the Mitsuda reaction, the evolution, progress and retrogression, the histological details and the prognosis.

Chapter V deals with typical acute tuberculoid leprides, or reaction leprides, as the authors style them, with a clinical subdivision into three forms, the nodular, the macular and the erythrodermic. Organisms are present and sometimes abundant in contrast with other forms of tuberculoid leprides. They tend to retrogression and spontaneous cure, usually in a short time, and nervous complications are few. On the other hand, they may become, as it were, stabilized, and the prognosis must, therefore, be guarded ; in respect of the two first points the prognosis is quite favourable, but the third is of graver significance. The Mitsuda reaction in 264 cases was strongly positive in 51 (19·3 per cent.), definite in 85 (32·2), weak in 60 (22·7), negative in 59 (22·3), doubtful in the other nine (3·4 per cent.). A table giving details of 51 patients with acute relapses states the initial form, the evolution and the later condition. Chapters VI and VII deal with atypical forms, those with gradual mutation to the tuberculoid and those of a more acute progression and the transition forms. The penultimate chapter is concerned with tuberculoid leprosy of the nerves, tuberculoid leprotic neuritis, of which the authors have notes of some 50 cases, with resultant anaesthesia following a period of hyperaesthesia. Caseation is a fairly common sequel, calcification very rare, with muscular atrophy and trophic lesions. The final chapter discusses the mixed cutaneous and nervous variety. Of the total of 966 cases of tuberculoid leprosy there were 185 (19·1 per cent.) of this mixed type. Very rarely cases

are met with—careful research and inquiry would probably discover more—in which the primary condition is lepromatous and then, after a long interval, the lesions retrogress and even disappear, leaving scars, and give place to the neuro-cutaneous form secondarily. There were only two such in the authors' list. A photograph of one of them is given and photomicrographs to show the histology of sections of the skin.

To sum up ; the work is a very careful and detailed, one might with justice call it a complete study of this aspect of leprosy. There are 109 illustrations all clearly reproduced and showing what the authors describe in the text ; the matter is well arranged, the clinical records aptly chosen and quotations fully authenticated. Each chapter has its references in footnotes and these are abundant. In short, this is an admirable piece of work and should be in the hands of all leprologists interested in the clinical and pathological aspects of tuberculoid leprosy. There is no index, but the contents of each chapter are given at the beginning of the book and also at the head of each chapter, so that a detailed index is not really needed. *H. Harold Scott*

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